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Volume 25 | Issue 1

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2015

# Defining Compensable Injury in Biomedical Research

Megan E. Larkin

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# DEFINING COMPENSABLE INJURY IN BIOMEDICAL RESEARCH

*Megan E. Larkin*<sup>†</sup>

## ABSTRACT

Biomedical research provides a core social good by enabling medical progress. In the twenty-first century alone, this includes reducing transmission of HIV/AIDS, developing innovative therapies for cancer patients, and exploring the possibilities of personalized medicine. In order to continue to advance medical science, research relies on the voluntary participation of human subjects. Because research is inherently uncertain, unintended harm is an inevitable part of the research enterprise. Currently, injured research participants in the United States must turn to the “litigation lottery” of the tort system in search of compensation. This state of affairs fails research participants, who are too often left uncompensated for devastating losses, and makes the United States an outlier in the international community. In spite of forty years’ worth of Presidential Commissions and other respected voices calling for the development of a no-fault compensation system, no progress has been made to date. One of the reasons for this lack of progress is the failure to develop a coherent ethical basis for an obligation to provide compensation for research related injuries. This problem is exacerbated by the lack of a clear definition of “compensable injury” in the biomedical research context.

This article makes a number of important contributions to the scholarship in this growing field. To begin, it examines compensation systems already in existence and concludes that there are four main definitional elements that must be used to define “compensable injury.” Next, it examines the justifications that have been put forth as the basis for an ethical obligation to provide compensation, and settles on retrospective nonmaleficence and distributive and compensatory justice as the most salient and persuasive. Finally, it uses the regulatory elements and the justifications discussed in the first two sections to develop a well-rounded definition of “compensable injury” that is tailored to the biomedical research context. Using this definition, it argues for the development of a first-of-its-kind no-fault compensation system in the United States.

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<sup>†</sup> Post-doctoral fellow, National Institutes of Health, Department of Bioethics; B.S. Emerson College; J.D. Boston University.

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## INTRODUCTION<sup>1</sup>

In March of 2006, eight healthy young male volunteers in London participated in a first-in-human trial of the novel monoclonal antibody TGN1412.<sup>2</sup> Animal studies indicated that TGN1412 was not likely to have lasting adverse biomedical effects.<sup>3</sup> Nonetheless, within ninety minutes of the drug's administration, the six volunteers randomized to the active arm of the trial suffered headaches, nausea, vomiting, and other symptoms.<sup>4</sup> Within twelve hours of the drug's administration, all six had suffered multi-organ failure and were in critical condition for several days.<sup>5</sup> Many suffered lasting injuries that left them unable to work and dependent on medical care.<sup>6</sup> The TGN1412 trial is a vivid example where research risks that seemed unlikely to occur materialized in a way that severely injured healthy volunteers.<sup>7</sup>

In 1993, five participants that had enrolled in U.S. clinical trials of an experimental Hepatitis B therapy, fialuridine, died as a result of

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1. This research was supported by the Intramural Research Program of the NIH, and the Warren G. Magnuson Clinical Center. The opinions expressed here are the views of the author. They do not represent any position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services. The author is a U.S. government employee who must comply with the NIH Public Access Policy, and the author or NIH will deposit, in NIH's PubMed Central archive, an electronic version of the final manuscript upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The author would like to thank Seema Shah, Alan Wertheimer, Ben Berkman, Leslie Meltzer Henry, Joe Millum, Kevin Outterson, Francis Miller, and Ron Ghatan for their thoughtful comments and helpful suggestions on previous drafts.
  2. Ganesh Suntharalingam et al., *Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, 355 NEJM 1018, 1018 (2006).
  3. *See id.* at 1027.
  4. *Id.* at 1018.
  5. *Id.*
  6. *See* Michael Seamark, "Elephant Man" Drug Trial Victim Set to Win £2m Payout for Horrific Injuries, DAILY MAIL, Apr. 29, 2008, <http://www.dailymail.co.uk/news/article-1015349/Elephant-Man-drug-trial-victim-set-win-2m-payout-horrific-injuries.html>.
  7. Elisabeth Rosenthal, *When Drug Trials Go Horribly Wrong*, N.Y. TIMES Apr. 7, 2006, <http://www.nytimes.com/2006/04/07/world/europe/07iht-drug.html>.

the administration of the study drug.<sup>8</sup> Because the subjects in the TGN1412 were in England, national laws and industry guidelines ensured that they would receive at least some compensation.<sup>9</sup> They ultimately received more damages by alleging negligence on the part of the company running the clinical trial.<sup>10</sup> The fialuridine trial subjects and their families, by contrast, were required to turn to the U.S. tort system “in search of compensation.”<sup>11</sup> The Institute of Medicine published a report on the trial that, in part, recommended that a no-fault compensation system for research injuries be developed in the United States.<sup>12</sup> To this date no progress has been made.<sup>13</sup>

Biomedical research provides a core social good that has dramatically improved the quality of life around the world.<sup>14</sup> As one commentator noted, “[e]xtremely serious and widespread diseases that plagued prior generations—yellow fever, polio, measles, diphtheria, and pertussis—have been almost eradicated through vaccines developed using complex and ground-breaking research.”<sup>15</sup> Research

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8. Robin McKenzie et al., *Hepatic Failure and Lactic Acidosis Due to Fialuridine (FIAU), An Investigational Nucleoside Analogue For Chronic Hepatitis B*, 333 NEJM 1099, 1099 (1995).
  9. See Seamark, *supra* note 6, at 2; Rosenthal, *supra* note 7, at 3 (noting that individuals may be eligible for £30,000 to £40,000 or more with permanent damages under relevant law, but that the sponsor only took out a £2 million insurance policy on the trial); but see Peter Mansell, *Window is Open for Compensation in TGN1412 Case*, CLINICAL NEWS (Mar. 14, 2007), [http://www.pharmatimes.com/article/07-03-14/Window\\_is\\_open\\_for\\_compensation\\_in\\_TGN1412\\_case.aspx](http://www.pharmatimes.com/article/07-03-14/Window_is_open_for_compensation_in_TGN1412_case.aspx) (stating that each participant had thus far received £10,000, but that they were hoping to obtain more by proving negligence).
  10. Seamark, *supra* note 6.
  11. COMM. TO REVIEW THE FIALURIDINE (FIAU/FIAC) CLINICAL TRIALS, REVIEW OF THE FIALURIDINE (FIAU) CLINICAL TRIALS 96 (Frederick J. Manning & Morton Swartz eds., 1995) (noting that while almost two million dollars had been spent on care for trial participants, many resorted to litigation “in search of compensation.”).
  12. *Id.*
  13. Leslie Meltzer Henry, *Moral Gridlock: Conceptual Barriers to No-Fault Compensation for Injured Research Subjects*, 41 J.L. MED. & ETHICS 411, 420-21 (2013).
  14. U.S. PRESIDENT’S COMM’N FOR THE STUDY OF ETHICAL PROBLEMS IN MED. & BIOMED. & BEHAVIORAL RESEARCH, COMPENSATING FOR RESEARCH INJURIES: THE ETHICAL AND LEGAL IMPLICATIONS OF PROGRAMS TO REDRESS INJURED SUBJECTS 9 [hereinafter U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF ETHICAL PROBLEMS] (1982). (“The power of medicine to cure and prevent illnesses has increased enormously during the [twentieth] century. All those having access to medical care have been the beneficiaries.”).
  15. Elizabeth R. Pike, *Recovering from Research: A No-Fault Proposal to Compensate Injured Research Participants*, 38 AM. J.L. & MED. 9, 10-11

also provides an evidence base for public health interventions that increase life expectancies and reduce morbidity and mortality.<sup>16</sup> In the twenty-first century, research continues to make progress in reducing transmission of HIV/AIDS,<sup>17</sup> developing innovative therapies for cancer patients,<sup>18</sup> and exploring the possibilities of personalized medicine.<sup>19</sup>

In order to provide society with the benefits of medical progress, the biomedical research enterprise relies on the voluntary participation of research subjects on whom new drugs and interventions are tested and whose normal biological processes are also studied.<sup>20</sup> Depending on the type of intervention being tested and the stage of the research, subjects may be either healthy volunteers from the community or individuals who currently suffer from the disease or condition that the study intervention is intended to alleviate. Research inherently exposes these subjects to risks—both known and unknown—associated with the study intervention, randomization, or research procedures.<sup>21</sup> Unintended harm is,

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(2012); *see also* U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 9.

16. *See, e.g.*, U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, MORAL SCIENCE: PROTECTING PARTICIPANTS IN HUMAN SUBJECTS RESEARCH 2 (Dec. 2011), *available at* <http://bioethics.gov/sites/default/files/Moral%20Science%20June%202012.pdf>.
17. *See* Myron S. Cohen et al., *Prevention of HIV-1 Infection with Early Antiretroviral Therapy*, 365 NEJM 493, 493 (2011).
18. *See, e.g.*, *Cancer Trends Progress Report – 2011-2012 Update*, NAT'L CANCER INST. 1, <http://progressreport.cancer.gov/doc.asp?pid=1&did=2011&mid=vc&chid=104> (last visited Nov. 19, 2014).
19. Margaret A. Hamburg & Francis S. Collins, *The Path to Personalized Medicine*, 363 NEJM 301 (2010).
20. U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 12-13.
21. *See id.*; *see also* U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 58. This is not intended to be an exhaustive list of possible sources of harm, but merely an illustration of some of the more common causes of harm. *See, e.g.*, Annette Rid & David Wendler, *A Framework for Risk-Benefit Evaluations in Biomedical Research*, 21 KENNEDY INST. ETHICS J. 141, 145-56 (2011) (setting forth a proposed framework for the analysis of research risks). It is not necessary at this point to distinguish between studies that pose a net risk to participants (where there is no prospect of direct benefit) and those where there is a prospect of direct medical benefit because the subject's motivation for participation does not affect the societal or scientific benefit that the research produces. Nor does it relieve researchers, sponsors, or institutions of their duty to minimize risks. *See, e.g.*, Steven Joffe & Franklin Miller, *Bench to Bedside: Mapping the*

therefore, an inevitable part of the research enterprise.<sup>22</sup> While rare,<sup>23</sup> tragedies like the death in 1999 of eighteen-year-old Jesse Gelsinger from an unforeseen complication in a gene-therapy trial and the death or disability of participants in the fialuridine trial at the National Institutes of Health in 1993,<sup>24</sup> have called national attention to the problem of biomedical research related injuries, but have not led to the creation of a comprehensive framework to provide compensation to those who are injured.

This lack of progress continues in spite of the work of several presidential and other commissions charged with examining the issue of compensation for biomedical research related injuries.<sup>25</sup> The subject was first raised in 1973 when the Department of Health Education and Welfare (DHEW) convened an ad hoc panel to address the ethical questions arising from the Tuskegee Syphilis Study.<sup>26</sup> Four

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*Moral Terrain of Clinical Research*, 38 HASTINGS CENT. REP. 30, 36 (2008) (stating that “[i]n research on healthy volunteers who have no prospect of medical benefit from research participation, nonmaleficence plainly does not require proportionality of risks and benefits for the subjects themselves. This lack of a requirement for proportionality is less obvious for sick patient-subjects, but it is still true. In both cases, it is both ethically justifiable and permissible, within appropriate limits, to expose research subjects to risks that are justified by the value of the knowledge to be gained from the research.”). *But see id.* (emphasizing also that researchers bear a duty of risk minimization within scientific constraints).

22. See, e.g., U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 56.
23. See Robert Steinbrook, *Compensation for Injured Research Subjects*, 354 NEJM 1871, 1871 (2006).
24. See Pike, *supra* note 15, at 7, 9; Sheryl Gay Stolberg, *The Biotech Death of Jesse Gelsinger*, N.Y. TIMES, Nov. 28, 1999, <http://www.nytimes.com/1999/11/28/magazine/the-biotech-death-of-jesse-gelsinger.html?pagewanted=all&src=pm>; see also Lawrence K. Altman, *The Doctor’s World; Fatal Drug Trial Raises Questions About ‘Informed Consent’*, N.Y. TIMES, Oct. 5, 1993, <http://www.nytimes.com/1993/10/05/science/the-doctor-s-world-fatal-drug-trial-raises-questions-about-informed-consent.html?pagewanted=all&src=pm>; Marlene Cimons, *The Deadly Risks of Research*, L.A. TIMES, Aug. 25, 1993, [http://articles.latimes.com/1993-08-25/news/mn-27830\\_1\\_drug-trials](http://articles.latimes.com/1993-08-25/news/mn-27830_1_drug-trials).
25. Henry, *supra* note 13, at 412.
26. U.S. DEP’T OF HEALTH, EDUC., AND WELFARE, FINAL REPORT OF THE TUSKEGEE SYPHILIS STUDY AD HOC ADVISORY PANEL 7 (1973), *available at* <http://biotech.law.lsu.edu/cphl/history/reports/tuskegee/report1.pdf>. See also ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS, FINAL REPORT 179 (1995), *available at* <https://ia700402.us.archive.org/10/items/advisorycommitte00unit/advisorycommitte00unit.pdf>; see also ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS, FINAL REPORT (1995),

years later, the 1977 DHEW Task Force on the Compensation of Injured Research Subjects concluded that research subjects were entitled to compensation if they suffered injuries that were proximately caused by research participation.<sup>27</sup> This was followed by the report of the 1982 President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which determined that there was justification for compensating injured research subjects, and that further study on the subject was needed.<sup>28</sup> The 1995 Advisory Committee on Human Radiation Experiments recommended the payment of financial remedies to injured subjects of the World War II-era human radiation experiments.<sup>29</sup> In 2001, the National Bioethics Advisory Committee found that, as a matter of justice, participants harmed "as a direct result of research should be cared for and compensated."<sup>30</sup> Most recently, in 2011, the President's Commission for the Study of Bioethical Issues released a report entitled "Moral Science," in which it argued that "subjects harmed in the course of human research should not individually bear the costs of care required to treat harms resulting directly from that research," and that the federal government should further study the need for a national compensation system.<sup>31</sup>

As is evident by the strikingly similar conclusions of the 1982 and 2011 reports, policy growth in this area has been staggeringly slow. Many bioethics commissions attribute the lack of progress to a dearth of empirical data on the frequency and severity of research related injuries.<sup>32</sup> Still, other authors have attributed the policy intransigence to "moral gridlock" in the form of disagreement over the ethical

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<https://ia600402.us.archive.org/10/items/advisorycommitte00unit/advisorycommitte00unit.pdf> (last accessed Aug 9, 2014).

27. U.S. DEP'T OF HEALTH, EDUC., & WELFARE, SECRETARY'S TASK FORCE ON THE COMPENSATION OF INJURED RESEARCH SUBJECTS VI-9 (1977), *available at* <http://babel.hathitrust.org/cgi/pt?id=mdp.39015034851611;view=1up;seq=48> (last visited Feb. 16, 2015).
28. *See* U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 4-5.
29. *See* ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS, *supra* note 26 at 801-05.
30. *See* NAT'L BIOETHICS ADVISORY COMM'N, 1 ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS, *at* v (2001).
31. U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 8.
32. *See, e.g.*, U.S. DEP'T OF HEALTH, EDUC., & WELFARE, *supra* note 27, at III-3; U.S. PRESIDENT'S COMM'N FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 5; U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 62.



justifications for compensation and what those justifications require of a compensation system.<sup>33</sup>

The United States is an outlier among nations in not requiring compensation for research related injuries.<sup>34</sup> The World Medical Association's Declaration of Helsinki states that it is a requirement of ethical human subjects research that, "[a]ppropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured."<sup>35</sup> The latest formulation of the Declaration is the first edition to include a requirement for compensation of research related injuries, and it is one indicator among many of a growing consensus among governments, policy-makers, and commentators that injured research participants are owed both medical care and financial compensation.<sup>36</sup>

Wide variation remains, however, in the reasons used to justify a requirement for compensation and the mechanisms of compensation used both by countries where research is conducted, and by research institutions themselves.<sup>37</sup> Additionally, different countries have taken multiple approaches to the problem of compensation for research related injuries.<sup>38</sup> These foreign approaches provide valuable guidance on how to define "compensable injury" in the United States and design a domestic system of compensation. Examination of international systems alone is, however, insufficient to justify the creation of a national compensation system. It is also necessary to undertake a robust examination of the ethical principles that justify a compensation requirement and to analyze how those ethical principles influence compensation systems already in place. This analysis should shape the design of any compensation system that is to be implemented in the United States.

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33. Henry, *supra* note 13, at 412-13.

34. Pike, *supra* note 15, at 39.

35. WORLD MED. ASS'N, DECLARATION OF HELSINKI, ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS 3 (2013), available at <http://www.wma.net/en/30publications/10policies/b3/>; see also Robert V. Carlson et al., *The Revision of the Declaration of Helsinki: Past, Present and Future*, 57 BRIT. J. CLINICAL PHARMACOLOGY 695, 699 (2004).

36. See, e.g., Pike, *supra* note 15, at 10; WORLD MED. ASS'N, *supra* note 35, at 3.

37. David B. Resnik et al., *Research-Related Injury Compensation Policies of U.S. Research Institutions*, 36(1) IRB 12, 13 (2014); U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 24; Christopher J. S. Hodges, *Research Injury in the European Community*, 5 PHARMA. MED. 135, 135 (1991).

38. See *infra* Part I; see also U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 57, 186-190.

The most pressing questions to come out of this process involve the definition of a “compensable injury.” Careful consideration of the justifications for providing compensation for research related injuries will define the contours of which injuries must be compensated by whom, and will aid in the development of a more comprehensive analytical framework.<sup>39</sup> A survey of both international compensation systems and past compensation proposals in the United States reveals that there are four essential elements that systems should consider in order to fully regulate the provision of compensation for research related injuries: causation, type, degree, and remedy.<sup>40</sup> Each element in this approach serves to define the contours of a compensable injury and to determine who owes what to whom.<sup>41</sup>

This article is the first to lay out a comprehensive definition of “compensable injury” that is both ethically justified and incorporates all four regulatory elements. To reach this conclusion, Part I examines systems of compensation that are already in operation both domestically and internationally. This analysis reveals that compensation systems vary in both their definition of “compensable injury” and their use of causation, type, degree, and remedy. The experience of international compensation systems reflects different justifications for the provision of compensation and should be used to inform the development of any compensation system in the United

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39. The origins of the contemporary bioethics movement are often traced to the promulgation of the Nuremberg Code in 1949 (Evelyn Shuster, *Fifty Years Later: The Significance of the Nuremberg Code*, 337 NEJM 1436, 1436 (1997)), the 1964 publication of the first version of the World Medical Association’s Declaration of Helsinki (Carlson et al., *supra* note 35, at 1), and within the United States, to the 1979 Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research [Belmont Report], National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Office of the Secretary, U.S. Department of Health, Education, and Welfare, 44 Fed. Reg. 23,192, 23,193-94 (Apr. 18, 1979) (codified at 45 CFR § 46), *available at* <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>. The Belmont Report, published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the wake of the 1974 National Research Act, set out three core principles that should guide those engaging in human subjects research: respect for persons, beneficence, and justice. These foundational ethical principles have been used to shape the norms currently found in many ethical codes and regulations governing the conduct of human subjects research. *See* Robert J. Levine & Angela R. Holder, *Legal and Ethical Problems in Clinical Research*, 7 CLINICAL RES. & REG. AFF. 315, 325 (1989).
40. *See, e.g.*, U.S. DEP’T OF HEALTH, EDUC., & WELFARE, *supra* note 27, at III-5; *see also* U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 57, 186-190.
41. *See* U.S. DEP’T OF HEALTH, EDUC., & WELFARE, *supra* note 27, at III-5.

States. Part II analyzes the justifications that have been put forth for compensation of research related injuries and argues that nonmaleficence and justice are the two most important. Part III uses the ethical justifications and the regulatory lessons developed earlier in the article to argue for a morally justified approach to defining compensable research injuries. It ends with a proposal for a compensation system that would fit with the justifications and definitions put forth.

## I. COMPENSATION SYSTEMS CURRENTLY IN EXISTENCE

### *A. International Compensation Systems*

Most countries that host or conduct a significant amount of research have policies in place that require researchers or sponsors to provide some level of compensation for treatment of participants' research related injuries.<sup>42</sup> International standard setting bodies such as the World Medical Association (WMA) and the Council for International Organizations of Medical Sciences (CIOMS) have also argued that compensation for research related injuries is a necessary component of ethical biomedical research.<sup>43</sup> A survey of international compensation systems reveals four main elements of regulating compensable research related injuries: cause, type, degree, and remedy.<sup>44</sup> Different nations use multiple combinations of these elements to determine which research related injuries are entitled to compensation.<sup>45</sup>

Within the international community, wide variation exists in the design of compensation systems used and the degree to which each system relies on each of the four regulatory elements. At a minimum, most nations have the requirement that the injury be causally related

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42. U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 57, 186-190.

43. *Id.*; *see also* COUNCIL FOR INT'L ORG. OF MED. SCI., INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS 78 (2002) ("Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants [sic] are entitled to compensation."); WORLD MED. ASS'N, *supra* note 35, at 3.

44. U.S. DEP'T OF HEALTH, EDUC. & WELFARE, *supra* note 27, at III-5 (discussing these same elements).

45. *See, e.g.*, U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 186-190; *see also* Drugs and Cosmetics (1st Amendment) Rules, 2013, Gazette of India, Part II, Sec. III (i) (Jan. 30, 2013) G.S.R. 53(E).

to the individual's research participation.<sup>46</sup> Some regulatory systems either limit or expand the class of eligible claimants by enumerating the types of injuries for which redress is required.<sup>47</sup> Other countries also limit compensation to physical injuries of a certain degree, for example, severe or disabling injuries.<sup>48</sup> Finally, a number of countries delineate the type and amount of remedy available.<sup>49</sup> It is useful to look at examples of countries that use different combinations of these four regulatory parameters in order to illustrate the interaction between the justifications for compensation identified above and the definitions of compensable injury chosen.

### 1. Simple Insurance Systems

Initially, it is noteworthy that many countries do not define in detail what constitutes a compensable research related injury and instead have a minimum insurance requirement that research sponsors must fulfill.<sup>50</sup> These simple insurance systems shift some or all of the cost of research related injuries on to sponsors and leave insurers to make determinations as to which injuries will be compensated.<sup>51</sup> Countries with simple insurance systems have varying levels of access to the courts for individuals who feel that compensation was

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46. See, e.g., Drugs and Cosmetics (1st Amendment) Rules, 2013, Gazette of India, Part II, Sec. III (i) (Jan. 30, 2013) G.S.R. 53(E) (India); India updated the Rules at the time this Article went to print. See Drugs and Cosmetics (1st Amendment) Rules, 2014, Gazette of India, Part II, Sec. III (i) (Dec. 12, 2014) G.S.R. 889(E) (India). See also, e.g., Henry Johansson, *The Swedish System for Compensation of Patient Injuries*, 115 UPSALA J. MED. SCIENCE 88, 88 (2010); see also Marie Bismark & Ron Paterson, *No-Fault Compensation In New Zealand: Harmonizing Injury Compensation, Provider Accountability, and Patient Safety*, 25 HEALTH AFF. 278, 280 (2006).
47. See, e.g., Johansson, *supra* note 46, at 88-90; see also Resolution N. 196/96, de 14 Janeriro de 1987, Risks and Benefits V.6 (Braz.).
48. See, e.g., SOUTH AFRICA DEP'T OF HEALTH, GUIDELINES FOR GOOD PRACTICE IN THE CONDUCT OF CLINICAL TRIALS WITH HUMAN PARTICIPANTS IN SOUTH AFRICA 1, 42 (2 ed. 2006), available at <http://www.kznhealth.gov.za/research/guideline2.pdf>.
49. See, e.g., Chieko Kurihara et al., *High Rate of Awarding Compensation for Claims of Injuries Related to Clinical Trials by Pharmaceutical Companies in Japan: A Questionnaire Survey*, 9 PLoS ONE e84998, 3 (2014).
50. See U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 186-90 (listing country compensation requirements from around the world. Countries with simple insurance requirements include: Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, France, Germany, Hungary, Iceland, Ireland, Italy, Lithuania, Latvia, Malta, Netherlands, Poland, Slovakia, Slovenia, Spain, United Kingdom, Brazil, Israel, Japan, Macedonia, Switzerland, Russia, and Ukraine).
51. See *id.*

inadequate.<sup>52</sup> At the opposite end of the spectrum, the United States and Canada simply require that research subjects be informed as to whether compensation will be made available, leaving to sponsors all determinations as to whether compensation will be provided.<sup>53</sup>

## 2. Causation

India is a prime example of a nation that regulates compensable research related injuries primarily based on a determination of what caused the injury. In a new compensation law passed in 2013, compensation is required for any injury or death of the subject occurring in the clinical trial for the following reasons:

- (a) adverse effect of investigational product(s);
- (b) violation of the approved protocol, scientific misconduct or negligence by the Sponsor or his representative or the investigator;
- (c) failure of investigational product to provide intended therapeutic effect;
- (d) use of placebo in a placebo-controlled trial;
- (e) adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;
- (f) for injury to a child in-utero because of the participation of parent in clinical trial; or
- (g) any clinical trial procedures involved in the study.<sup>54</sup>

In light of concerns about the conceptual definition of the compensation requirements<sup>55</sup> and the effect the requirements were

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52. See, e.g., *Law Concerning Experiments on the Human Person*, Art. 29 (Belgium, 2004), <http://www.erasme.ulb.ac.be/page.asp?id=11365&langue=EN#a29> (requiring insurance coverage for liability and also allowing for access to the courts).
53. See 45 C.F.R. § 46.116(a)(6) (2001); Tri-Council Policy Statement, *Ethical Conduct for Research Involving Humans*, 1, 3-5 (2010), <http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter3-chapitre3/#toc03-1a>.
54. Drugs and Cosmetics (1st Amendment) Rules, 2013, Gazette of India, Part II, Sec. III (i) § 2 1, 9 (Jan. 30, 2013) (India).
55. See REPORT OF THE RANJIT ROY CHANDHARY EXECUTIVE COMMITTEE TO FORMULATE POLICY AND REMOVAL OF NEW DRUGS CLINICAL TRIALS AND BANNING OF DRUGS 15 (2013) [hereinafter CHAUDHARY REPORT], available at [http://cdsco.nic.in/writereaddata/Report\\_of\\_Dr\\_Ranjit\\_Roy.pdf](http://cdsco.nic.in/writereaddata/Report_of_Dr_Ranjit_Roy.pdf).

having on India's research industry,<sup>56</sup> recent regulatory reforms have tempered the compensation requirement and built upon an expert report commissioned by India's Central Drug Standards Control Organization.<sup>57</sup> The new regulations require, among other things, consideration of whether the standard of care was provided to trial subjects when determining whether an injury is compensable.<sup>58</sup> Although the *de minimus* causation requirement is the most noteworthy facet of India's 2013 law, the regulations also contain requirements with respect to the types of injury covered and the remedy owed.<sup>59</sup> Although causation comes to the foreground when discussing India's compensation regulations, the other regulatory elements are present, if less pronounced.

### 3. Type

Brazil, by contrast, broadens the class of eligible claimants by including all types of injury that may result from research participation. Brazil's regulations require that "[r]esearch subjects that suffer any type of injury resulting from their participation in research . . . have the right to receive comprehensive medical care, as well as indemnity."<sup>60</sup> Research injuries are defined as "immediate or delayed injury to an individual or community, with proven, direct or indirect, causal relationship resulting from the scientific study."<sup>61</sup> And risks of research are defined as "possibility of injury to the physical, psychic, moral, intellectual, social, cultural, or spiritual dimensions of the human subject, during any phase of an investigation, or resulting therefrom."<sup>62</sup> Brazil regulates not just by cause, but also by type of injury, which includes a broad range of injuries that may be

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56. J. Sugarman, et al., *India's New Policy to Protect Research Participants*, 347 BMJ f4841, at 1 (2013).
57. See CHAUDHARY REPORT, *supra* note 55, at 6-8; Megan E. Larkin, *Acoustic Separation and Biomedical Research: A Case Study of Indian Regulations on Compensation for Research-Related Injuries*, J. LAW, MED., & ETHICS (forthcoming 2015) (manuscript at 1-4) (on file with author).
58. See CHAUDHARY REPORT, *supra* note 55, at 3, 6-7, 85.
59. See generally GSR 53(E), *supra* note 54; see also Drugs and Cosmetics (1st Amendment) Rules, 2013, Gazette of India, Part II, Sec. III (i) 63(E) § 2 1, 4 (Jan. 30, 2013) (India); see also Drugs and Cosmetics (3rd Amendment) Rules, Gazette of India, Part II, Section III (i) (India) G.S.R. 73(E) (2013).
60. Nat'l Health Council Resolution No. 196/96 on Research Involving Human Subjects § V.6 (1996) (Bra.) [hereinafter N.H.C. Res. No. 196/96]; see also Pike, *supra* note 15, at 42.
61. N.H.C. Res. No. 196/96 at II.9.
62. *Id.* at II.8.

considered compensable if found to be suitably research related (*i.e.*, having a direct or indirect causal relationship to the research). Examination of regulations like Brazil's is important because it raises the question of whether injuries other than physical and financial ones should be considered compensable in light of the justifications for providing compensation.

#### 4. Degree

A third type of regulation considers the degree of injury (in addition to causation and type) in order to determine which injuries are compensable. For example, the Association of the British Pharmaceutical Industry (ABPI) guidelines recommend compensation where "[o]n the balance of probabilities, the injury was attributable to the administration of a medicinal product under trial or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the Participant in the trial."<sup>63</sup>

The ABPI guidelines further counsel that "[c]ompensation should only be paid for the more serious injury of an enduring and disabling character . . . and not for temporary pain or discomfort or less serious or curable complaints."<sup>64</sup> While these guidelines are voluntary, in practice they are widely followed. Additionally, when deciding whether to approve a research proposal, ethics committees are instructed to consider whether provision has been made for compensation in the event of serious injury or death.<sup>65</sup> Notably, compensation is limited to those circumstances where care alone does not remedy the injury.<sup>66</sup> A number of countries have modeled their compensation requirements on the ABPI guidelines.<sup>67</sup>

#### 5. Remedy

Japan has based its system of compensation largely upon the ABPI guidelines. It departs from the ABPI model because it contains a more detailed definition of what amount of compensation is required

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63. THE ASS'N OF BRITISH PHARM. INDUS., CLINICAL TRIAL COMPENSATION GUIDELINES 4 (2014), *available at* [http://www.abpi.org.uk/our-work/library/guidelines/Documents/compensation\\_guidelines\\_2014.pdf](http://www.abpi.org.uk/our-work/library/guidelines/Documents/compensation_guidelines_2014.pdf) (last visited Apr. 8, 2014).

64. *Id.*

65. *See, e.g.*, THE ASS'N OF BRIT. PHARM. INDUS., INSURANCE AND COMPENSATION IN THE EVENT OF INJURY IN PHASE I CLINICAL TRIALS 4-5 (2012), <http://www.abpi.org.uk/our-work/library/guidelines/Pages/clinical-trials-insurance.aspx> (last visited Aug. 12 2014); *see also* Medicines for Human Use (Clinical Trials) Regulations, 2004, S.I. 2004/1031, art. 3, ¶ 15(5)(i) (U.K.).

66. *See* S.I. 2004/1031, Part 3, cl. 15(5)(i) (U.K.); *see also* Pike, *supra* note 15, at 62.

67. Pike, *supra* note 15, at 42.

for different types of injuries.<sup>68</sup> Japan's standards for compensation are based on those of the Industrial Accident Compensation Insurance Act, and cover the participant's costs up to a certain limit (about 70 percent) in exchange for the participant not having to prove negligence.<sup>69</sup> The formula used to calculate the amount of damages owed includes the type and degree of injury and the participant's earning capacity prior to the injury.<sup>70</sup> The damages calculated under the formula are deemed to be those that would have been available had the participant taken the case to court.<sup>71</sup> Those damages are then reduced by 30 percent.<sup>72</sup> The justification for this reduction is that in lieu of the full amount of damages theoretically available through the legal system, the participant will receive payment quickly.<sup>73</sup> One commentator has raised concerns that participants in therapeutic research or in phase one studies designed to test drugs that produce some benefit at the end of life may be underserved by the current calculation of damages because of their diminished earning capacity.<sup>74</sup> Recently, however, pharmaceutical companies have been narrowing the definition of compensable injuries to limit available compensation for less serious injuries (as judged by type and degree).<sup>75</sup> Compensation is made available through insurance purchased to cover such losses.<sup>76</sup> Notably, such insurance is not required in all clinical trials thus leaving some gaps in the compensation available to participants depending on what type of trial they are enrolled in.<sup>77</sup>

#### 6. Comprehensive Medical Injury Compensation Systems

A few nations have well-developed compensation systems that incorporate research related injuries into a larger national framework for compensation of medical injuries.<sup>78</sup> These frameworks take into

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68. See Tatsuo Kuroyanagi, *Compensation and Insurance for Participants/Subjects Harmed in Clinical Research Studies: Process of the Inheritance of Good Clinical Practice (GCP) in Japan and its Present Status*, 56 JPN. MED. ASSOC. J. 458, 460-61 (2013).

69. *Id.* at 461-62.

70. *Id.*

71. *Id.* at 461.

72. *Id.*

73. *Id.*

74. *Id.*

75. *Id.*

76. *Id.* at 461-62.

77. *Id.* at 463-64.

78. See, e.g., Patient Injury Act, S-155.87, 9<sup>th</sup> Riksdag (Swed. 1996), available at [http://www.patientforsakring.se/resurser/dokument/engelska\\_artiklar/](http://www.patientforsakring.se/resurser/dokument/engelska_artiklar/)



consideration all four elements of defining an injury and provide a method for determining which injuries are eligible for compensation.<sup>79</sup> Sweden and New Zealand both provide interesting examples of how such a framework may be set up, and they provide useful lessons for those considering implementing a robust system of compensation.

Sweden's system of compensation for medical injuries is premised on the concept of "avoidability," which is defined as a medically necessary action that, according to later evaluation, could have been avoided by using another available procedure that would have met the current research need in a less risk-filled manner. Avoidability is determined from a medical viewpoint in accordance with accepted standards observed by experienced researchers within the area concerned.<sup>80</sup> Actions performed solely for research purposes are considered not medically necessary and are therefore entitled to compensation.<sup>81</sup> Payment is provided through the Patient Insurance Association, which assures the same level of coverage for all public institutions in Sweden.<sup>82</sup> Injuries caused by medication may be covered by either the Patient Insurance Association or by separate pharmaceutical insurance depending on the etiology of the injury.<sup>83</sup> Claims may be reviewed by the Patient Claims Panel, which is designed to support fair and consistent interpretation of the Patient Injury Act. The Panel may also issue opinions at the request of a claimant, provider, insurer, or court.<sup>84</sup> Participants retain a right of action in the courts throughout the claims process.<sup>85</sup>

Compensable injuries are defined as personal injuries that are either physical or mental, so long as the mental injury produces a "medically demonstrable effect."<sup>86</sup> All injuries must, "with

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The\_Patient\_Injury\_Act.pdf; *see also* Section 2 of the Accident Compensation Act of 2001, as substituted by Section 10 of the Injury Prevention, Rehabilitation, and Compensation Amendment Act 2005 (N.Z.), *available at* <http://www.legislation.govt.nz/act/public/2001/0049/latest/DLM99494.html?src=qs> (last visited Aug. 11, 2014) [hereinafter Accident Compensation Act].

79. The Patient Injury Act, S-155.87, 9<sup>th</sup> Riksdag, § 10 (1996); *see also* Section 2 of the Accident Compensation Act 2001, *supra* note 78.
80. *See* ULF HELLBACHER ET AL, PARTICIPANT INJURY COMPENSATION FOR HEALTHCARE-RELATED INJURIES 20-21 (2007).
81. *Id.* at 23.
82. *Id.* at 14.
83. *Id.* at 39-40.
84. *Id.* at 14.
85. *Id.* at 15.
86. *Id.* at 17.

preponderant probability be caused by measures or conditions” of treatment in order to be compensable.<sup>87</sup> “Direct consequences of the underlying disease and injuries that would have occurred or developed anyway, regardless of medical care, are therefore not eligible for compensation.”<sup>88</sup> Most injuries do not have a limit for compensation based on degree, but injuries caused by infections must be of a type not reasonably expected to be tolerated by a patient in order for it to be compensable.<sup>89</sup> Compensation is also available for accident related injuries if they are “related to and typical of healthcare activities.”<sup>90</sup> Injuries due to inadequate information or failure to obtain consent are handled under the general tort law framework.<sup>91</sup> Compensation under the Patient Insurance Act is equal to 80 percent of damages for the injury as calculated under Section 1 of the Tort Liability Act.<sup>92</sup>

New Zealand’s system differs slightly from that implemented in Sweden in both its method of financing compensation and the criteria used to define “compensable injury.” Unlike Sweden’s system, which relies on mandatory insurance, New Zealand has adopted a publically funded system for compensating people with personal injuries that replaces its tort system.<sup>93</sup> New Zealand’s Injury Prevention, Rehabilitation, and Compensation Act allows coverage for, among other things, “treatment injuries caused as part of a clinical trial.”<sup>94</sup> In order for compensation to be available, an ethics committee must have approved the trial and have been satisfied that the trial was not conducted “principally for the benefit of the manufacturer or distributor of the medicine or item being trialed.”<sup>95</sup> Participants injured during a trial that was not approved by an ethics committee or in a trial conducted principally for the benefit of the manufacturer or distributor have the right to sue for negligence.<sup>96</sup> Treatment injuries that are compensable are defined as “adverse medical events

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87. *Id.* at 19.

88. *Id.*

89. *Id.* at 33.

90. *Id.* at 39.

91. *Id.* at 42.

92. *See id.* at 51-53 (reducing the remedy by “one twentieth of the base amount under the National Insurance Act (1962:381)” under section 9 and an additional 15% under section 16).

93. Bismark & Paterson, *supra* note 46, at.278.

94. HEALTH RESEARCH COUNCIL OF NEW ZEALAND, GUIDELINES ON ETHICS IN HEALTH RESEARCH 1, 31 (2005), <http://www.hrc.govt.nz/news-and-publications/publications/ethics-and-regulatory>.

95. *Id.*

96. *Id.* at 32.

that must be causally linked to the treatment (but do not require a finding of fault) and are not a necessary part or ordinary consequence of the treatment.”<sup>97</sup> Treatment injuries do not include those due to the participant’s underlying health condition, those solely attributable to resource allocation decisions, or those due to the participant’s “unreasonably withholding or delaying their consent to treatment.”<sup>98</sup> Covered injuries include death, physical injury, mental injury suffered by a person because of physical injury, and damage to dentures or prostheses.<sup>99</sup>

Claims under the system are processed through the Accident Compensation Corporation (ACC) national claims unit.<sup>100</sup> If participants are unsatisfied with the determination of their claim, they may request a review of the claim and also retain a right of appeal to a court.<sup>101</sup> Under the Act, treatment and rehabilitation “includes the cost of pharmaceuticals, disability aids, child care, home modifications, and vocational retraining.”<sup>102</sup> Most health care treatment costs are already covered by the country’s universal health care system.<sup>103</sup> Compensation for lost earnings includes “weekly compensation of 80 percent of the claimant’s earnings at the time of injury, up to a set maximum,” and lump sum compensation up to a set cap is available for injuries resulting in permanent impairment.<sup>104</sup> Support for dependents in the event of a participant’s death is also available.<sup>105</sup> Since 2005, New Zealand does not use degree of injury when determining whether an injury is compensable.<sup>106</sup> Of course, the level of compensation available depends on the degree of impairment suffered.<sup>107</sup>

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97. *Id.* at 31.

98. New Zealand Injury Prevention, Rehabilitation, and Compensation Act, Public Act 2005 No. 2 § 32(4), 47<sup>th</sup> Parliament (N.Z. 2005) *available at* [http://www.legislation.govt.nz/act/public/2005/0045/latest/DLM347084.html?search=sw\\_096be8ed80ce33e0\\_research\\_25\\_se&p=1](http://www.legislation.govt.nz/act/public/2005/0045/latest/DLM347084.html?search=sw_096be8ed80ce33e0_research_25_se&p=1) (last visited Apr. 18, 2014).

99. *Id.* at §26(1).

100. Bismark & Paterson, *supra* note 46, at 280.

101. *Id.*

102. *Id.*

103. *Id.*

104. *Id.* at 280-81.

105. *Id.* at 281.

106. *Id.* at 280 (describing adoption of “treatment injury” in the 2005 reforms).

107. *See id.* at 280-81.

New Zealand's public compensation system notwithstanding, the New Zealand Researched Medicines Industry has promulgated its own guidelines that are modeled on those of the ABPI.<sup>108</sup> The guidelines require payment of appropriate compensation (no less than that available under the ACC) on a no-fault basis to research participants whose injuries are due—on the balance of the probabilities—to their participation in a clinical trial.<sup>109</sup> Injuries due to the failure of the studied product to have its intended effect, administration of licensed medications or placebos in the control arm, departures from the agreed protocol, wrongful conduct by a third party, or contributory negligence by the participant are not covered.<sup>110</sup> This agreement voluntarily shifts the cost of compensation for industry-sponsored trials to industry rather than to the government of New Zealand.

Sweden and New Zealand's approaches include several elements that should be incorporated into any compensation system. Importantly, both systems include an initial determination by an expert in the field, a uniform system of compensation that is objective and easily applicable, and procedural protections including a right to appeal.<sup>111</sup> Both systems have thorough statutory and regulatory underpinnings that clearly define (1) the class of eligible claimants, (2) which injuries should be covered, and (3) what remedies are available.<sup>112</sup> While the approaches of both Sweden and New Zealand come from a context in which broad social welfare programs exist, their methods for sorting out thorny issues such as causation should be considered when deciding what a no-fault research related injury compensation system in the United States might look like.<sup>113</sup>

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108. *Regulation of Clinical Trials*, MEDICINES N.Z., <http://www.medicinesnz.co.nz/clinical-trials/> (last visited Apr. 18, 2014).
109. RESEARCHED MEDICINES INDUS. ASS'N OF N.Z., RESEARCHED MEDICINES INDUSTRY GUIDELINES ON CLINICAL TRIALS COMPENSATION FOR INJURY RESULTING FROM PARTICIPATION IN AN INDUSTRY-SPONSORED CLINICAL TRIAL, §3, at 3 (Aug. 2008), *available at* <http://www.medicinesnz.co.nz/assets/Uploads/compensation-guidelines-0808-final.pdf>.
110. *Id.* This should be contrasted with the approach taken in India's 2013 regulations, which *do* require compensation for the failure of the intervention to have its intended effect, departure from the agreed protocol, wrongful conduct of investigators, and in spite of any potential contributory negligence by the participant/subject. *See* GSR 53(e), *supra* note 54.
111. *See supra* notes 80, 94, 98, 100 and accompanying text.
112. *See id.*
113. Indeed, some commentators have argued that Sweden's system should be replicated in the United States. Allen B Kachalia et al., *Beyond Negligence: Avoidability and Medical Injury Compensation*, 66 SOC. SCI. MED. 387, 387 (2008).

## 7. Lessons from the International Community

Examples from the international community illustrate the fact that the most complete frameworks for compensation of research related injuries define injuries using all four regulatory elements: cause, type, degree, and remedy. Considering all four elements is important because any system that discounts one or more of them lacks the definitional clarity that is necessary for a compensation system to be both ethically grounded and practically functional. Systems that have less well-rounded definitions of what injuries are compensable often leave the definitional questions to insurers or other non-state parties which gives those parties the power to limit the criteria for compensation in ways that are inconsistent with the justifications underlying a compensation requirement.<sup>114</sup> A clear definition of compensable injury that incorporates all four regulatory elements gives research participants notice of what injuries will be covered and to what extent.<sup>115</sup> A clear definition also has the advantage of ensuring that like cases are treated alike, and that participants with similar injuries are not treated differently based on arbitrary factors like the location of the study or a lack of guidance.

The problems associated with a lack of definitional clarity are evident in the American approach to compensation for research related injuries. The Common Rule requires only that research participants be informed as to whether compensation is available, and it does not even attempt to define what would constitute a compensable injury.<sup>116</sup> As a result, the question is left to individual institutions and insurers, resulting in wide variability in the remedies available.

### *B. Domestic Compensation Systems*

The United States has no uniform requirement for compensation of research related injuries.<sup>117</sup> The Code of Federal Regulations requires only that research participants be made aware of whether compensation is available for research related injuries during the informed consent process.<sup>118</sup> Different institutions within the United

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114. See Larkin, *supra* note 57.

115. See Leslie Meltzer Henry et al., *Just Compensation: A No-Fault Proposal for Research Related Injuries* (forthcoming 2015) (manuscript at 20) (on file with the author).

116. 45 C.F.R. § 46.116(a)(6) (2013).

117. *Id.* (“For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.”).

118. *Id.*

States therefore create and implement their own compensation policies.<sup>119</sup> The lack of uniform agreement on compensation has led to widespread variation in the availability of compensation for research related injuries.<sup>120</sup> In the past twelve years, there has been virtually no change in the number of institutions offering compensation for research related injuries in the United States.<sup>121</sup> It continues to be the case that, of the institutions for which data is available, more than half offer no compensation and only 5 percent offer unconditional compensation.<sup>122</sup> The result of this patchwork approach to compensation is that research participants' ability to receive compensation for research related injuries is almost entirely dependent on where they are enrolled in research.<sup>123</sup> This is even true among participants enrolled at different research sites in the same trial.<sup>124</sup>

Within institutions, the availability of compensation may depend on the sponsor of the clinical trial.<sup>125</sup> Many academic institutions that host clinical trials require industry sponsors to provide compensation for research related injuries, but do not require government or non-profit sponsors to do the same.<sup>126</sup> Because there is no reliable no-fault mechanism for compensation of research related injuries, most participants must turn to the tort system in hope of recovery.<sup>127</sup> The tort system is widely regarded as inadequate to meet the need for compensation for research related injuries because it requires proof of culpable conduct on the part of sponsors or investigators and there are numerous other barriers to compensation for many classes of research participants.<sup>128</sup>

The availability of coverage varies widely among institutions that provide care or compensation for research related injuries. For example, the Department of Veterans' Affairs, National Institutes of Health, and the Department of Defense provide free, short-term medical care for all research related injuries, but other compensation

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119. Resnik et al., *supra* note 37, at 2.

120. *Id.*

121. *Id.* at 6.

122. *Id.*

123. *Id.* at 2.

124. *Id.*

125. See Michael K. Paasche-Orlow & Frederick L Brancati, *Assessment of Medical School Institutional Review Board Policies Regarding Compensation of Subjects for Research-Related Injury*, 118 AM. J. MED. 175, 179 (2005).

126. *Id.*

127. Pike, *supra* note 15, at 43-44.

128. *Id.*

is not available.<sup>129</sup> Since 2000, Medicare has paid for care for injured patient/participants (not healthy volunteers) who are Medicare beneficiaries.<sup>130</sup> These systems ignore factors related to the type and degree of injury and have only a bare-bones causation requirement coupled with a specification of the type of remedy available—namely, medical care.<sup>131</sup> In the wake of the Affordable Care Act, private insurers are now also required to pay for participation in clinical trials for cancer or similarly life threatening diseases, but whether this payment extends to coverage for research related injuries is unclear.<sup>132</sup>

Until mid-2014, the University of Washington was widely regarded as having one of the most robust systems of compensation for research related injury. It defined a research related injury as a bodily injury, and stated that:

[E]xcept in special circumstances, the term does not include impairment of mental processes or emotional distress, nor does it encompass effects resulting from: (1) injuries from diagnostic or therapeutic procedures, either standard or experimental, performed as part of patient management; (2) the normal course of a disease or condition; or (3) non-compliance with study procedures.<sup>133</sup>

This is a developed definition that sets forth the type of injury covered and some limitations on the cause of the injury.<sup>134</sup> Compensation under the original University of Washington system

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129. 38 U.S.C. § 501 (2014); 38 C.F.R. § 17.85 (2014) (“VA medical facilities shall provide necessary medical treatment to a research subject injured as a result of participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees.”). The VA does not cover injuries caused by subject non-compliance with study procedures. *Id.*; 32 C.F.R. §108.4(i) (2014); U.S. DEP’T OF DEF., DIRECTIVE 3216.02 26 (2011), *available at* <http://www.dtic.mil/whs/directives/corres/pdf/321602p.pdf>; *see also* Pike, *supra* note 15, at 25.

130. Pike, *supra* note 15, at 25.

131. 38 C.F.R. § 17.85; 32 C.F.R. § 108.4(i).

132. 42 U.S.C. § 300gg-8 (2012). *See also Insurance Coverage for Clinical Trial Participants*, AM. SOC. CLINICAL ONCOLOGY, <http://www.asco.org/insurance-coverage-clinical-trial-participants> (last visited Mar 27, 2015).

133. UNIV. OF WASH., HUMAN SUBJECTS MANUAL 7, *available at* <http://staff.washington.edu/brz/MANUAL/99-VII.htm> (last visited Apr. 24, 2014).

134. *See id.*

was limited to the cost of care, and it failed to factor in economic damages.<sup>135</sup>

The University of Washington system was revised in September 2014 in part to “accommodate numerous changes in health care systems.”<sup>136</sup> The changes restrict the availability of compensation to only healthy volunteers in clinical trials.<sup>137</sup> This removes patient/participants from the pool of eligible claimants and precludes compensation for most individuals enrolled in research that has a prospect of direct medical benefit to the research participant.<sup>138</sup> The new policy also caps the amount of medical reimbursement at \$250,000.<sup>139</sup> While the change to this policy is understandable in light of the current climate of the health care market, it reflects a setback for institutions attempting to provide coverage to injured research participants.

As these examples demonstrate, the compensation available to American research subjects—when there is compensation at all—is similar in structure to that available in much of Europe.<sup>140</sup> It is either insurance or self-insurance that covers the cost of medical care.<sup>141</sup> American systems largely lack compensation for economic damages and long-term disability.<sup>142</sup> These systems, for the most part, do not attend to all four regulatory elements instead leaving core definitional determinations to third parties.

## II. RETROSPECTIVE NONMALEFICENCE AND DISTRIBUTIVE AND COMPENSATORY JUSTICE AS JUSTIFICATIONS FOR COMPENSATION

In the past four decades, a number of scholars have put forth justifications for compensating research related injuries.<sup>143</sup>

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135. *Id.*

136. *Revised Injury Compensation Program*, UNIV. OF WASH. HUMAN SUBJECTS DIV. (Sept. 15, 2014) <http://www.washington.edu/research/hsd/announcements/?q=1645>.

137. *Id.*

138. *Id.*

139. *Id.*

140. *See, e.g.*, ABPI Guidelines 2001, *supra* note 63, (describing sponsor-based insurance of costs. It is similar to the University of Washington system in terms of the structure, but is far more comprehensive in its definition of what is covered and in the compensation available).

141. *See supra* Part I.A.

142. *See* 38 C.F.R. § 17.85; *see also* 32 C.F.R. § 108.4(j); U.S. DEP’T OF DEF., *supra* note 129, at 26; UNIV. OF WASH, *supra* note 133, at 8.

143. *See, e.g.*, Levine & Holder, *supra* note 39, at 1; *see also* David B. Resnik, *Compensation for Research-Related Injuries, Ethical and Legal*



Justifications have included theories based in beneficence,<sup>144</sup> nonmaleficence,<sup>145</sup> distributive justice,<sup>146</sup> compensatory justice,<sup>147</sup> and cost-shifting.<sup>148</sup> These proposed justifications often pull in different directions and do not always align with the means of compensation contemplated.<sup>149</sup> The justifications also diverge with respect to the definition of what constitutes a research related injury and when such an injury should be compensable.<sup>150</sup> It is therefore necessary to determine which justifications are warranted, and what those justifications imply for the definition of a research related injury and how that injury should be remedied. This requires reasoning from the principles underlying biomedical research ethics and applying them to the distinct problem of research related injuries.<sup>151</sup> In particular, it is important to engage in this exercise to understand what harms compensation should address and to ensure that the means of redress are consonant with the aims.<sup>152</sup> The ethical principles underlying a compensation requirement help to define the universe of eligible claimants, determine which injuries are covered, and identify the appropriate remedy.<sup>153</sup>

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*Issues*, 27 J. LEG. MED. 263–87 (2006); Henry, *supra* note 13, at 411–412 (noting the variety of justifications for compensation that have been put forth).

144. Resnik, *supra* note 143, at 265–66.

145. See, e.g., Joffe & Miller, *supra* note 21, at 36.

146. U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 58.

147. Levine & Holder, *supra* note 39, at 343.

148. See, e.g., Guido Calabresi, *Some Thoughts on Risk Distribution and the Law of Torts*, 70 YALE L. J. 499, 514 (1961).

149. See, e.g., Clark C. Havighurst, *Compensating Persons Injured in Human Experimentation*, 169 SCIENCE 153, 153–57 (1970); Alan J. Weisbard, *On Not Compensating for Bad Outcomes to Biomedical Innovation*, 8 CARDOZO L. REV. 1161, 1167–69 (1987); Henry, *supra* note 13, at 412.

150. See *infra* Part II.

151. See, e.g., TOM L. BEAUCHAMP & JAMES F. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS* 12 (Oxford Univ. Press, 6th ed. 2009).

152. See, e.g., G. Owen Schaefer & Alan Wertheimer, *The Right to Withdraw From Research*, 20 KENNEDY INST. ETHICS J. 329, 330 (2010) (discussing the importance of providing a moral foundation for the right to withdraw).

153. See *infra* Part III.

Obligations to provide compensation<sup>154</sup> and care<sup>155</sup> to injured research subjects can be found in the core ethical principles of nonmaleficence (closely linked to, but distinct from, beneficence) and justice. As argued below, each principle supports different, though overlapping obligations to provide compensation for research related injuries, and each principle places the obligation of compensation on a different actor.

*A. Retrospectivity, Beneficence, and Nonmaleficence*

Beneficence and nonmaleficence are often regarded as paired obligations. Beneficence is a moral obligation to act to benefit others.<sup>156</sup> The duty of beneficence “rest[s] on the mere fact that there are other beings in the world whose condition we can make better.”<sup>157</sup> If not limited in some way, an obligation of beneficence would be difficult to apply because it is potentially boundless.<sup>158</sup> Stronger duties of beneficence may, therefore, arise based on an individual’s role relationship; for example, a doctor or a clinical researcher may have general duties of beneficence to their patients or research participants.<sup>159</sup> A general duty of beneficence is applicable in the research context, but such a duty does not create an obligation to provide compensation for research related injuries.<sup>160</sup> This is so because the general duty of beneficence can be discharged in other ways.<sup>161</sup> Broadly put, “rules of beneficence state positive requirements of action, need not always be followed impartially, and rarely, if ever, provide moral reasons that support legal punishment when agents fail

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154. “Compensation” is used throughout this piece to refer to monetary compensation, which should include compensation for the cost of medical care.
155. “Care” and “treatment” are used interchangeably throughout this piece to refer to medical care.
156. Ezekiel J. Emanuel et al., *What Makes Clinical Research Ethical?*, 283 JAMA 2701, 2706 (2000); BEAUCHAMP & CHILDRESS, *supra* note 151, at 197.
157. DAVID DEGRAZIA ET AL, BIOMEDICAL ETHICS 25 (7th ed. 2010) (quoting W.D. Ross).
158. *See, e.g.*, BEAUCHAMP & CHILDRESS, *supra* note 151, at 197-99 (attempting to narrow and define an obligatory account of beneficence).
159. *See id.* at 205.
160. Henry, *supra* note 13, at 416.
161. *See* Tom Beauchamp, *The Principle of Beneficence in Applied Ethics*, in THE STANFORD ENCYCLOPEDIA OF PHILOSOPHY 5-6 (Edward N. Zalta ed., 2013), *available at* <http://plato.stanford.edu/archives/win2013/entries/principle-beneficence/> (last visited Aug. 5, 2014).

to abide by the rules.”<sup>162</sup> The general duty of beneficence, therefore, provides a reason for providing benefit to research subjects, but does not specify that the benefit must be in the form of compensation for research related injuries.

Notwithstanding the generally weak form of the duty of beneficence, there are some instances in which a strong duty of beneficence applies.<sup>163</sup> The most widely agreed upon of these is the duty to rescue. The duty to rescue requires that an individual “make efforts to rescue strangers under conditions of minimal risk.”<sup>164</sup> For example, consider a case where A is on the bank of a river, and B has fallen in. There is a life preserver next to A on the bank of the river that A could toss to B (saving B’s life) with little or no risk to A. In such a case, the perfect duty of beneficence would counsel that A has an obligation to throw the life preserver to B.

The perfect duty of beneficence found in the duty to rescue does not, however, imply an obligation to compensate for research related injuries. This is because the payment of compensation is not a rescue scenario. The injury has already occurred at the time compensation would be given, and any peril from a lack of compensation is not imminent. The duty to provide emergent medical care is adequately covered by researchers’ obligation of nonmaleficence, and any need for compensation is separate and apart from the subject’s medical needs.

Duties of nonmaleficence, in contrast to those of beneficence, “rest on the complementary fact that [one] can also make the condition of other beings worse . . . [and can be] summed up under the heading of ‘not injuring others.’”<sup>165</sup> Nonmaleficence in the context of biomedical research “requires that researchers who work with human subjects strive to minimize, consistent with the scientific aims of their research, the risks and burdens their experimental procedures impose.”<sup>166</sup> Unlike beneficence, a duty of nonmaleficence in research specifically requires compensation for injury as a way to minimize the risks imposed on subjects.<sup>167</sup> Nonmaleficence, as spelled out in greater detail below, is both prospective and retrospective; it requires

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162. *Id.* at 5.

163. *Id.* at 6.

164. *Id.* at 5.

165. DEGRAZIA ET AL., *supra* note 157, at 25.

166. Joffe & Miller, *supra* note 21, at 36.

167. BEAUCHAMP & CHILDRESS, *supra* note 151, at 153 (“Obligations of nonmaleficence include not only obligations not to inflict harms, but also obligations not to impose *risks* of harm. A person can harm or place another person at risk without malicious or harmful intent, and the agent of harm may or may not be morally or legally responsible for the harms.”).

minimization of foreseeable risks of research and also minimization of the effects that risk taking has on research subjects.

The duty of risk minimization is limited, in principle, by the requirement that risks be minimized only to the extent consistent with the scientific aims of the research.<sup>168</sup> The Common Rule, recognizing that risk elimination is not feasible, requires only that institutional review boards (IRBs) ensure that research presents a reasonable risk-benefit profile.<sup>169</sup> In particular, it is widely accepted that “it is both ethically justifiable and permissible, within appropriate limits, to expose research subjects to risks that are justified by the value of the knowledge to be gained from the research.”<sup>170</sup> Reasonable limits on risk minimization may stem from concerns about cost, subject autonomy, or scientific integrity. These limits notwithstanding, provision of care and compensation is necessary to both maximize possible benefits and also minimize possible harms.<sup>171</sup> It can be accomplished without attempting to eliminate risks entirely, or taking the principle of risk minimization to an extreme.<sup>172</sup>

There are different types of risk to which the principle of nonmaleficence and the corresponding duty to minimize risk might apply. The two most salient are biomedical and financial. It is well accepted that both types of risk should be considered when determining which research to undertake, and whether an injured participant may be entitled to compensation.<sup>173</sup> The boundaries of the

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168. See Joffe & Miller, *supra* note 21, at 36.

169. See, e.g., 45 C.F.R. § 46.111 (2013) (detailing the Common Rule criteria for IRB approval of research); see also DEP’T OF HEALTH, EDUC. & WELFARE, THE BELMONT REPORT (1979), available at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html#xassess>; see also the *Nuremberg Code*, stating “that the degree of risk ‘should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.’” quoted in Pike, *supra* note 15, at 15.

170. Joffe & Miller, *supra* note 21, at 36.

171. See *infra* Section II. See also Larkin, *supra* note 57, at 5.

172. A full account of the boundaries of an obligation to minimize risks is beyond the scope of this article, but it is clear that within those boundaries there remains a strong duty to engage in risk minimization, and there is a role for compensation to play in fulfilling this duty.

173. See, e.g., Rid & Wendler, *supra* note 21, at 149 (stating that “potential harms of all types—physical, psychological, social, and economic,” should be considered when conducting a risk-benefit analysis), Charles Weijer, *The Ethical Analysis of Risk*, 28(4) J. L., MED. & ETHICS 344, 346 (2000) (identifying four types of risk: physical, psychological, social, and economic); see also Richard S. Saver, *Medical Research and Intangible Harm*, 74 U. CIN. L. REV. 941, 944-946 (2006) (discussing intangible harms of medical research).

duty to minimize risk are somewhat ill-defined, but they do not counsel against a definition of risk that encompasses both biomedical and financial harm.<sup>174</sup> The aim of a definition of risk should be to ensure that the risk-benefit calculus accurately reflects the costs of the research. Providing prompt medical care minimizes biomedical risks,<sup>175</sup> while paying for that care minimizes financial risks.<sup>176</sup>

Under the current framework for regulation of biomedical research, institutional review boards (IRBs) play an important role in risk minimization and participant protection.<sup>177</sup> They are tasked with evaluating the risks and benefits of a proposed study, and with ensuring that the research proposed presents a favorable risk-benefit profile. In many other countries, IRB<sup>178</sup> review includes an assessment of whether provision has been made for compensation in the event of a research related injury, but in the United States, such an analysis is not required.<sup>179</sup> IRBs also have a central role in approving the process for obtaining informed consent to research and ensuring that potential participants are adequately informed of the risks and benefits attendant to participation.<sup>180</sup> These measures are a form of prospective nonmaleficence—the forward-looking minimization of possible harms before the research begins.

Reliance on IRBs to mitigate or eliminate all potential harms of research, however, risks overstating both their role and their

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174. In fact, the financial risk to research participants has historically been considered as a reason for their compensation. *See, e.g.*, Pike, *supra* note 15, at 18-20 (examining the historical reasons given for compensation, which include concerns over financial harm to research subjects).

175. Minimization of biomedical risks may also help avert future financial risks by avoiding the need for more medical care.

176. *See, e.g.*, D. R. Vagstad et al., *Protecting the Uninsured Human Research Subject*, 6(6) J. PUB. HEALTH MGMT. PRACTICE 37, 37 (2000). *See also* Resnik, *supra* note 143, at 266. *See also* D. U. Himmelstein et al., *MarketWatch: Illness and Injury as Contributors to Bankruptcy*, 2 HEALTH AFF. W5-63 (2005).

177. *See* Emanuel et al., *supra* note 156, at 2701.

178. In other countries boards that perform the same function as IRBs may go by different names, for example, Research Ethics Committees (RECs) or Ethics Committees. *See, e.g.*, Drugs and Cosmetics (First Amendment) Rules (2013) GAZETTE OF INDIA, Part II - Section 3 - Sub-section (i) G.S.R. 53(E).

179. *See, e.g.*, Medicines for Human Use (Clinical Trials) Regulations, 2004 S.I. 1031 (U.K.); *see also* U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 186-90.

180. Emanuel et al., *supra* note 156, at 2701.

institutional competence.<sup>181</sup> IRB approval alone does not ensure that research is conducted in an ethically appropriate manner, or that subjects are adequately informed of the risks of participation, particularly when explicit consideration of the financial risks of participation is not necessarily part of the ethical analysis conducted by either researchers or the IRBs that oversee them.<sup>182</sup> Provision of IRB review of clinical trials does not, therefore, eliminate the need for compensation in the case of injury, which provides a different and supplemental type of protection. In particular, concerns related to retrospective nonmaleficence—mitigating the effect of harm that has already occurred—are not incorporated in the current IRB review process.

One objection to the risk-based argument in favor of compensation is that subjects who give their informed consent to participate in research assume the risks inherent in that research and make a gift of themselves to society.<sup>183</sup> On its face, this argument is attractive because people are allowed to assume many risks in their day-to-day lives. For example, people are permitted to assume the risk of sports such as skiing and commonly waive liability before they take to the slopes.<sup>184</sup> Underlying the assumption of risk argument and its appeal is the notion that people may freely assume risks when they have knowledge of the risks and voluntarily give their informed consent to undertake them.<sup>185</sup> Arguments about assumption of risk

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181. See Seema K. Shah, *Outsourcing Ethical Obligations: Should the Revised Common Rule Address the Responsibilities of Investigators and Sponsors?*, 41 J.L. MED. & ETHICS 397, 397 (2013).

182. See *id.*

183. See U.S. PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 53-56. It should be acknowledged that this argument may be more salient in the case of altruistic research participation and that it is potentially inapplicable in "net benefit" research where the subject at the time of enrollment has a prospect for direct biomedical benefit from clinical trial participation. In such cases there is considerable doubt as to whether the research participant intends to make a gift of him or herself to society.

184. See generally C. Connor Crook, JD, *Validity and Enforceability of Liability Waivers on Ski Lift Tickets*, 28 CAMPBELL L. REV. 107, 107-121 (2005) (surveying state laws regarding the validity and enforceability of lift ticket waivers); see also Karen E. Crummy, *Colorado Ski Industry Enjoys Protection From Law, Waivers*, DENVER POST, Mar. 3, 2013, [http://www.denverpost.com/ci\\_22813161/colorado-ski-industry-enjoys-protection-from-law-waivers](http://www.denverpost.com/ci_22813161/colorado-ski-industry-enjoys-protection-from-law-waivers).

185. See U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 59.

are, however, misapplied to the question of compensation for research related injury.<sup>186</sup>

Research subjects are not well positioned to make good decisions about when to assume risks in research, and when to avoid them. As the President's Commission stated:

[I]n helping to advance research, human subjects sometimes place themselves in a position of informational asymmetry, where they must rely on the expertise and wisdom of researchers, reviewers, funding institutions, and, at times, their own physicians to ensure that a research study in which they enroll is designed and deployed with their rights and welfare in mind.<sup>187</sup>

Informational asymmetry may mean that subjects do not necessarily have a full or accurate appreciation of the risks of the research they are participating in, even after they have gone through the informed consent process.<sup>188</sup> Risks, as they appear in biomedical research, "are a function of two more basic components: (1) the likelihood that a harmful event or experience will occur as a result of an intervention, and (2) the extent to which the event or experience, should it occur, sets back the individual participant's interests."<sup>189</sup> Risk evaluation requires both an empirical judgment "about how robust and relevant the available data are regarding the potential harms and benefits of the interventions," and a normative judgment of whether the magnitude of the risk to the individual is justified by

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186. The Secretary's Task Force (1977) concluded that, "informed consent does not negate or waive the obligation to provide compensation. The case is similar to that of persons who have been injured in the course of voluntary military service. The fact that a person has volunteered does not eliminate that person's right to be compensated in the event of injury, whether or not the injury was foreseeable. The Task Force agrees that consent should not negate the rights of research volunteers. Informed consent in the research setting functions as a recognition of and a protection for a person's integrity and autonomy, but does not imply a waiver of the right of the person to compensation in the event of injury." HEW SECRETARY'S TASK FORCE ON THE COMPENSATION OF INJURED RESEARCH SUBJECTS, *supra* note 27.

187. U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 70.

188. See, e.g., U.S. PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 58-59. ("Remote risks of serious harms are especially likely to attend experimental procedures. Consent in such cases is necessarily somewhat blind, and true appreciation of cases is necessarily somewhat blind, and true appreciation of risk is doubtful, even for ideally competent subjects.").

189. Rid & Wendler, *supra* note 21, at 148-49.

the potential for the research to benefit society.<sup>190</sup> There is ample room for an individual participant to either misapprehend or misevaluate the nature of the known risks of proposed research participation, or the likely value of his or her research participation to the advancement of medical science.<sup>191</sup>

While subjects may not have a full understanding or appreciation of the risks of research, sponsors and research institutions are better positioned to understand these risks. Current guidelines and standards require researchers to weigh the risks of research against the risks of “comparator activities,” such as those encountered in daily life or ordinary medical care.<sup>192</sup> Such an evaluation should consider both the physical and economic risks that a given research activity poses.<sup>193</sup> That some financial risk accompanies a research related injury is foreseeable by the study sponsor or research institution, and the financial risk can be offset by those same institutions that are best placed to identify and avoid it.<sup>194</sup> Researchers and sponsors have an obligation to weigh the risk to individual subjects against the value of the research, and will be better able to determine when the risk is unacceptably high such that it is not worth conducting the research at all.

Often the full risks of participation in medical research are unknown, even to the researchers themselves.<sup>195</sup> One way to minimize

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190. *Id.* at 143.

191. *Id.* at 145 (arguing that “[d]etermining that a study achieves a minimum level of social value requires detailed knowledge of the research topic, as well as knowledge of the scientific methods proposed in the study.”).

192. Annette Rid et al., *Evaluating the Risks of Clinical Research*, 304 JAMA 1472, 1472-73 (2010).

193. *Id.*

194. *See, e.g.* Schaefer & Wertheimer, *supra* note 152, at 337-38. While researchers may not be in a perfect position to make individualized judgments about the impact of financial risk on any particular research participant, certain generalizations about the impact of financial risk may be applicable. For example, low-income or uninsured individuals are likely to suffer much more if a financial risk materializes than higher-income individuals who may have the ability to take paid sick leave or rely on a disability insurance policy. Even with these differences, however, the risk mitigation strategy is the same: free care and compensation for financial injury should the risk materialize.

195. *See, e.g.*, D.R. Vasegard et al., *supra* note 176, at 45; WENDY MARINER, COMMITTEE ON ETHICAL AND LEGAL ISSUES RELATING TO THE INCLUSION OF WOMEN IN CLINICAL STUDIES & INSTITUTE OF MEDICINE, WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 117 (1994); U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 58; *see also* U.S. PRESIDENT’S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 9-10.



the net effects<sup>196</sup> of unknown or unknowable risks is to ensure that subjects exposed to such risks do not have to pay the full cost of treatment if the risks are realized and require medical care.<sup>197</sup> Viewed this way, the financial risk is separate from the medical risk, and the net effects of that risk are subject to mitigation through guaranteed compensation. As has been argued in the context of the right to withdraw from research, “[g]iven that informed consent is insufficient to protect subjects from misjudging the full costs of participating in a study, society may prefer to protect individuals from the consequences of their nonculpable misjudgments.”<sup>198</sup> When reasonable compensation for research related injuries is guaranteed, injured research subjects are protected from both unforeseen and underappreciated risks. Medical care can be incredibly expensive, and, depending on the financial resources of the participant, can lead to significant financial harm, such as bankruptcy.<sup>199</sup> Compensation is therefore aligned with the requirements of the principle of nonmaleficence as applied in biomedical research. No other approach can adequately shield research subjects from bearing the full weight of unforeseen or underestimated risks while simultaneously providing a financial incentive for study sponsors and institutions to engage in proactive risk minimization.

Even a general duty to minimize risks, aside from the issue of compensation, is open to criticism. Benjamin Sachs argues that the requirement of risk minimization is an example of bioethics “exceptionalism” because we do not require risk minimization in analogous relationships, such as those between employers and employees or volunteer organizers and volunteers.<sup>200</sup> In particular, Sachs contends that the “distinction between necessary and unnecessary risks is largely absent from our moral reasoning about the employer-employee relationship,” and that we primarily concern ourselves with whether employees are adequately compensated for

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196. The net effects of a risk are the ways in which the risk materializes for the affected individual, for example, by causing an injury that requires further medical care or days off from work.

197. See, e.g. Resnik, *supra* note 143, at 266 (relying on beneficence as the root of the same risk minimization obligation and arguing that “[i]f a subject has been harmed by a research-related injury, beneficence obligates researchers to try to minimize the additional harms that may occur to the subject as a result of the injury. Researchers can fulfill this obligation by providing the subject with medical care or financial compensation.”).

198. Schaefer & Wertheimer, *supra* note 152, at 338.

199. Himmelstein, *supra* note 176.

200. Benjamin Sachs, *The Exceptional Ethics of the Investigator-Subject Relationship*, 35 J. MED. PHILOS. 64, 70 (2010).

taking those risks.<sup>201</sup> While Sachs concedes that the duty to minimize risks and concern over necessary versus unnecessary risks reemerges in the context of volunteer-organizer/volunteer relationships, he concludes that exceptionalism of this type is difficult to defend because it fails to treat morally analogous relationships alike with the result of imposing restrictions on research that are not ethically necessary.<sup>202</sup>

Sachs's argument is flawed because it is based on a faulty premise. Society does require risk management in the employment context. Regulatory bodies like OSHA regularly mitigate the risks to which employers may expose their employees.<sup>203</sup> Workmen's compensation reduces the financial hazards associated with irreducible workplace risks.<sup>204</sup> When a job is viewed as unacceptably risky, it is open to judgment that it should either be changed to reflect a more favorable risk-benefit profile, or it should be discontinued.<sup>205</sup> The example by which Sachs chooses to illustrate his point is particularly demonstrative. He cited the National Football League as an example of allowing individuals to knowingly accept the risks of a job, without any obligation on the part of the employer to minimize those risks.<sup>206</sup> As the recent scandal over the risk of traumatic brain injury in football demonstrates, there is a concern that the risks of head injury are not "necessary" to the sport of football, and a legal and ethical obligation has been placed on the NFL to study and minimize the risks of concussion going forward, and to compensate players who are currently suffering from the lasting effects of traumatic brain injury.<sup>207</sup>

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201. *Id.*

202. *Id.* at 70-71, 75.

203. See U.S. DEP'T LABOR, OSHA LAW AND REGULATIONS, *available at* <https://www.osha.gov/law-regs.html> (last visited Oct. 18, 2014).

204. See, e.g., U.S. DEP'T OF LABOR, WORKERS' COMPENSATION, *available at* <http://www.dol.gov/dol/topic/workcomp> (last visited Oct. 18, 2014).

205. Of course, it is possible that we as a society allow people to take on greater risks in the employment context than as participants in biomedical research because individuals may be financially compensated for taking riskier jobs. It is much more contentious, however, whether *ex ante* financial compensation is appropriate to offset the risks of research participation. See generally Christine Grady, *Payment of Clinical Research Subjects*, 115 J. CLIN. INVEST. 1581, 1581 (2005).

206. Sachs, *supra* note 200.

207. See Ron Winslow, *NFL Union Funds Study of Injury Risk*, WALL ST. J., Jan. 29, 2013, <http://www.wsj.com/articles/SB10001424127887323644904578270212095595572> (last visited Apr. 22, 2015). See, e.g., *Editorial: What Players' Brain Damage Will Cost the NFL*, CHI. TRIB., July 15, 2014, <http://www.chicagotribune.com/news/opinion/editorials/ct-national->

The requirement to minimize risks in the researcher-participant relationship is not, therefore, an example of bioethics exceptionalism, but rather a specific execution of a principle broadly applicable to similar relationships in our society.

Nonmaleficence, as argued above, creates an obligation to provide compensation for research related injuries. The next question to be answered is then, who bears the duty generated by the principle of nonmaleficence? As previously argued, nonmaleficence requires first that those conducting or sponsoring the research not intentionally cause harm, and second, that the risks of participation in research be minimized.<sup>208</sup> Nonmaleficence, as applied in the research setting, holds that there is a stronger duty to act when there is a duty of care.<sup>209</sup> It therefore places the duty to compensate research subjects at the feet of the sponsors of medical research and the institutions that conduct it. Of the possible duty bearers, these entities are best positioned to minimize the risks to research participants because they have the best understanding of the risks inherent in the research and the evidentiary base underlying the testing of any intervention. They are also in the best position to make appropriate financial or risk spreading arrangements so that the net effects of risk may be mitigated rather than being borne entirely by the injured research participants.

### *B. Justice*

An obligation to provide compensation for research related injury is also supported by the principle of justice. In particular, three different formulations of the principle of justice—compensatory, distributive and reparative—support a requirement for compensation. Underlying these concerns is the fact that “[u]nintended harm is inevitable in the course of human subjects research,” and although the benefits of research are shared broadly, the risks fall almost exclusively upon those who volunteer to be research subjects.<sup>210</sup>

Distributive justice “refers to fair, equitable, and appropriate distribution [of resources that must] be determined by justified norms that structure the terms of social cooperation.”<sup>211</sup> As applied to compensation for research related injury, it suggests that benefits should be distributed in a manner that accounts for the

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football-league-concussion-edit-20140715-story.html (last visited Oct. 18, 2014).

208. See BEAUCHAMP & CHILDRESS, *supra* note 151, at 149-155.

209. See, e.g., Joffe & Miller, *supra* note 21, at 36.

210. U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 58.

211. BEAUCHAMP & CHILDRESS, *supra* note 151, at 226.

disproportionate burden borne by some research subjects. Compensatory justice, in a related vein, is concerned with compensation for risks undertaken on behalf of others.<sup>212</sup> Reparative justice, by contrast, is a form of corrective justice that is intended to repair an injury wrongfully caused by the actions of another.<sup>213</sup> Discussed below are the ways in which the different justice concerns translate into an obligation to compensate participants for research related injuries.

### 1. Distributive and Compensatory Justice

At its core, the principle of distributive justice is concerned with the distribution of scarce benefits in competitive environments, and with the distribution of burdens that are borne by a subset of an overtly similar class.<sup>214</sup> In a more particularized formulation, “[t]he principle of distributive justice requires that those who take the risks of research should receive the benefits.”<sup>215</sup> As Wendy Mariner explains:

Compensation is a means of redressing the imbalance between the risks undertaken by research subjects and the benefits. Since most legitimate research is intended to benefit society as a whole, the subject assumes the risks for society’s sake (some would say making a gift to society). Therefore, society has a moral obligation to make the injured subject whole by compensating those who took the risks and suffered thereby.<sup>216</sup>

Risks are theoretically distributed evenly among research participants selected without prejudice. The harm to a participant who is actually injured, however, may be either ameliorated or exacerbated by the participant’s background conditions. In countries and health systems where there is no social safety net and the cost of medical care is borne largely by the individual participant, the magnitude of the risk of any given research injury is dependent on individual factors that are to some extent uncontrollable by the research sponsor or institution. For example, the cost of care for a research related injury may have a disproportionately large impact on an individual who does not have many financial resources, or who is

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212. See Henry, *supra* note 13, at 417.

213. *Id.* at 413 (reparative justice is “a form of corrective justice intended to make an injured party whole again, but while compensation counteracts a loss or harm that may not be due to any wrongdoing, reparations ‘repair’ an injury to one party that is wrongfully caused by another.”).

214. Levine & Holder, *supra* note 39, at 328.

215. MARINER, *supra* note 195, at 116.

216. *Id.*

uninsured.<sup>217</sup> Health insurance also does not guarantee that a patient will not suffer significant costs associated with a research related injury, as coverage and coverage caps will vary between plans.<sup>218</sup> Even in countries with partial or full safety nets, available medical care may not make the injured participant whole again in light of other costs of the injury, such as time lost from work or continuing disability.<sup>219</sup> The level of risk undertaken by each participant in a study could be more evenly distributed through provision of financial compensation for research related injuries because external financial factors would be controlled for, leaving the inevitable biomedical differences as the primary source of differences in individual risk burden.

Compensatory justice has slightly different theoretical underpinnings than distributive justice, but reaches much the same result. Compensatory justice is rooted in the principle of fairness and aims to compensate individuals for risks undertaken on behalf of others.<sup>220</sup> This is the justification that has historically found the most support in the work of presidential commissions,<sup>221</sup> and it is the justification for well-established compensation systems currently in place in the United States. It “does not presuppose wrongful injury [(there is no award of damages)], but is a matter of restitution and restoration sometimes by the community as a whole . . . .”<sup>222</sup> Compensatory justice takes “account of a previous state of affairs and attempt[s] to restore a ‘fallen’ individual or group to it.”<sup>223</sup> Compensatory justice also does not take into account the motivation of the research participant when determining whether compensation is owed.<sup>224</sup> This is so because whether the participant enrolls for self-interested or civic-minded reasons, the public benefit produced by the

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217. See Himmelstein, *supra* note 176.

218. See Jonathan Gruber, *Growth and Variability in Health Plan Premiums in Insurance Market Before the Affordable Care Act*, COMMONWEALTH FUND (June 5, 2014), <http://www.commonwealthfund.org/publications/issue-briefs/2014/jun/health-insurance-premiums>.

219. See, e.g., Johansson, *supra* note 46 (setting forth a comprehensive scheme for compensating medical injuries through both treatment and financial remedies).

220. James F. Childress, *Compensating Injured Research Subjects: I. The Moral Argument*, 6(6) HASTINGS CENT. REP. 21, 22 (1976). See Henry et al., *supra* note 115, at 12.

221. Henry, *supra* note 13, at 417.

222. Childress, *supra* note 220.

223. *Id.*

224. *Id.*

advancement of medical science is the same.<sup>225</sup> The results of the research are similarly irrelevant to the question of compensation because even studies that have negative results produce a social benefit.<sup>226</sup>

The compensatory justice account of compensation for research related injury provides a convincing rationale for existing programs that provide benefits to individuals who are injured in the service of society.<sup>227</sup> Two salient examples are the provision of benefits to veterans and the creation of the National Vaccine Injury Compensation Program (VICP).<sup>228</sup> Veterans in the United States are entitled to financial compensation for disabilities that are either caused or aggravated by their military service.<sup>229</sup> This benefit has historically applied to both draftees and volunteers alike.<sup>230</sup> The VICP, on the other hand, compensates individuals who are injured due to vaccination. The program provides compensation to individuals harmed in the process of creating herd immunity through widespread vaccination, which benefits to the public at large.<sup>231</sup>

Each of these programs is funded in a different manner, but they have the same underlying ethical justification, namely, when individuals have benefitted society and become injured in the process, these systems work to spread the costs of compensating the injured parties among the class of beneficiaries. Similarly, in research, science and the development of new therapeutic treatments would not be able to go forward without the participation of human research subjects. With research comes an “ineliminable burden” of risk.<sup>232</sup> Risks borne

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225. *Id.*

226. *Id.*

227. *See id.*

228. *See* U.S. DEP’T OF HEALTH AND HUMAN SERVS., NATIONAL VACCINE INJURY COMPENSATION PROGRAM, <http://www.hrsa.gov/vaccinecompensation/index.html> (last visited Oct. 18, 2014). *See also* U.S. CT. OF FED. CLAIMS, VACCINE CLAIMS/OFFICE OF SPECIAL MASTERS, <http://www.uscfc.uscourts.gov/vaccine-programoffice-special-masters> (last visited Oct. 18, 2014). *See also* Childress, *supra* note 220.

229. *See* U.S. DEP’T OF VETERANS’ AFFAIRS, COMPENSATION, <http://www.benefits.va.gov/COMPENSATION/types-compensation.asp> (last visited Oct. 18, 2013).

230. Childress, *supra* note 220.

231. U.S. DEP’T OF HEALTH & HUMAN SERVS., HUMAN RES. & SERVS. ADMIN., WHAT YOU NEED TO KNOW ABOUT THE NATIONAL VACCINE INJURY COMPENSATION PROGRAM (2011), <http://www.hrsa.gov/vaccinecompensation/84521booklet.pdf>.

232. U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 59 (quoting Daniel Wikler & Mary Saltonstall, Compensation for Research-Related Injury – Presentation to the PCSBI

by research participants to benefit society at large should be both minimized and distributed fairly.<sup>233</sup> Compensation for research related injury is a risk spreading mechanism because it forces society at large to bear a portion of the cost of that risk of injury.<sup>234</sup>

While the obligation created by distributive and compensatory justice is spread more broadly than the one created by the principle of nonmaleficence, it demands less of each individual on whom it falls.<sup>235</sup> A duty of this nature would be satisfied by some publicly funded compensation system akin to veterans' benefits or the VICP. A compensation system that is based on a theory of distributive and compensatory justice should therefore place at least some of the burden of payment for research related injury on the public at large.

The burden of distributive and compensatory justice also falls upon the shoulders of research sponsors and institutions to the extent that these entities benefit financially or otherwise from the commercialization of the products of biomedical research. Because these entities reap a portion of the financial benefits of a new drug, device, or intervention, they hold an obligation in distributive and compensatory justice to the individuals who suffer a research related injury.<sup>236</sup>

## 2. Reparative Justice

Reparative justice is based on the premise that a party that has injured another is responsible for correcting or mitigating the harm caused. Currently, compensation for research related injury is often left to the legal system in the form of civil tort suits.<sup>237</sup> This is a classic embodiment of the principle of reparative justice because "[t]he tort system requires injured research subjects to prove not only that

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(Nov. 17, 2011), *available at*  
<http://bioethics.gov/sites/default/files/Meeting%207%20Session%208.pdf>.

233. See Henry, *supra* note 13, at 417-19.

234. See *id.*

235. See U.S. PRESIDENT'S COMM'N FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 51, 56-57 (recognizing that an argument from the principle of justice creates a relatively weak societal obligation).

236. See Resnik, *supra* note 143, at 282 ("Private sponsors benefit from the profits they earn selling biomedical products, such as drugs or medical devices. Research institutions benefit from the contracts and grants they receive from private or government sponsors to conduct research, which compensate institutions for the direct and indirect costs of doing research . . . . Research subjects also often benefit from research, because they may receive medical care or other therapy, educational materials, or money. However, if a subject is injured in research, the burdens for that subject may far outweigh the benefits.").

237. See Pike, *supra* note 24, at 23.

the research study *caused* their injury, but that *fault* for the injury lies with the research team, pharmaceutical company, or institutional sponsor.”<sup>238</sup> While the reparative justice framework provides an adequate justification for compensation where the research participant has been harmed because of some sort of misconduct by the sponsor, institution, or researcher, it does not address the issue of compensation where a research related injury is not the product of negligence or an intentional tort.<sup>239</sup> Given the uncertainty inherent in conducting research on novel medical interventions or strategies, or applications of existing interventions or strategies, injuries will occur in research even when sponsors and researchers do nothing wrong.<sup>240</sup> Such injuries do not create a claim in reparative justice and are not susceptible to redress through the tort system.<sup>241</sup> Claims that are based in negligence or malfeasance should be channeled into the tort system for appropriate redress, but claims that are not the product of wrongful action ought to be dealt with through an alternative no-fault compensation system.

*C. Pragmatic Reasons for Compensating Research Related Injuries*

In addition to the ethical reasons for providing compensation for research related injuries, there are also practical benefits. In particular, compensation could have the positive effect of increasing enrollment in human subjects research.<sup>242</sup> Research is necessary for the advancement of medical treatment and care, and even studies that do not produce positive outcomes or results contribute to the knowledge base available to future researchers.<sup>243</sup> Compensation for research related injury gives participation in any given study a more favorable personal risk-benefit profile and may remove one large disincentive to participation—the possibility of having to pay for medical treatment.<sup>244</sup> A uniform policy favoring compensation would also have the benefit of harmonizing the different compensation policies currently in existence and providing research subjects with a universal

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238. Henry, *supra* note 13, at 413.

239. *See id.*

240. *See, e.g.,* BEAUCHAMP & CHILDRESS, *supra* note 151, at 155.

241. Pike, *supra* note 24, at 29.

242. *See* U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 61.

243. *See* U.S. PRESIDENT’S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS, *supra* note 14, at 8-9.

244. *See* U.S. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 61-62.



baseline level of protection that does not depend on the location of the study.<sup>245</sup>

As Alex John London has observed, “research is an enterprise that uses social resources to provide social benefits.”<sup>246</sup> London argues that public confidence in research is reduced when the problems of “antipathy, disrespect, lack of social value, or unfair division of social resources” arise in the research process.<sup>247</sup> In particular, antipathy, as used by London, “refers to a manifest lack of concern for the health, welfare, and broader interests of research participants.”<sup>248</sup> By failing to provide compensation for research related injuries, the current research enterprise exhibits just such antipathy toward the individuals who volunteer to become research subjects. Creation of a national no-fault compensation system might, therefore, have the added benefit of fostering public support for the continuation of the research enterprise.<sup>249</sup>

#### *D. Application*

As demonstrated above, the justifications for compensating subjects for research related injuries place the duty to provide compensation on different actors. The principles of nonmaleficence and reparative justice place the duty at the feet of the research sponsors, institutions, and investigators. By contrast, the principles of distributive and compensatory justice place the duty on the beneficiaries of the research, be that either society at large or the research sponsors and institutions that stand to profit from the eventual commercialization of any knowledge gained by the research enterprise. A compensation system can be designed to allocate the primary burden of compensation among different potential duty bearers. It need not, however, always stay there. Primary duty bearers may distribute the duty among other potential duty bearers. For example, if sponsors are responsible for providing compensation, the cost of that compensation may be built in to the market price of the therapeutic intervention that the research helped to produce. If research institutions are responsible, the cost may be built in to the charges they pass on to sponsors (and thus distributed to the public

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245. *Id.* at 62.

246. Alex John London, *A Non-Paternalistic Model of Research Ethics and Oversight: Assessing the Benefits of Prospective Review*, 40 J. LAW. MED. ETHICS 930, 943 (2012).

247. *Id.* at 933.

248. *Id.*

249. *See, e.g., id.* at 935 (arguing that “[a] tipping point is reached when the reservoir of public trust is significantly diminished and social support for the research enterprise is called into question or revoked.”).

through the pricing of any intervention), or incorporated in the cost of receiving medical care at that institution.

In light of the multiple ways that the burden of compensation could be distributed, any framework for compensation should incorporate consideration of the justifications for compensation and where those justifications place the duty to compensate. Reparative justice, when it applies, provides the strongest justification for compensating research related injuries. It is a foundational principle of the tort system and a widely accepted principle in law and ethics that one who wrongfully injures another has an obligation to make that person whole.<sup>250</sup> Cases in which reparative justice requires compensation are, however, relatively rare because the injured party must prove that the injury was wrongful.<sup>251</sup> A wrongful injury is one that is the product of a culpable state of mind—negligence, recklessness, or intent—on the part of the one who causes the injury. These cases are appropriately dealt with through the tort system, which is designed to provide a mechanism for those who have been wronged to seek monetary damages from the one who wronged them.<sup>252</sup> Any duty to compensate based in reparative justice, therefore, should not be dealt with in a new compensation system, but would be better handled by reforms to the existing tort framework.

A recent article enumerates the many barriers to compensation for research related injury under the current tort law framework.<sup>253</sup> It argues that the tort system “is an unsatisfactory compensation mechanism for almost all litigants” because it “is time-consuming, adversarial, expensive, and has a tendency to under-compensate most injured participants while over-compensating a select few.”<sup>254</sup> Injured research participants face high barriers to recovery due to lack of established case law and difficulty proving a breach of a legal duty owed to them or that the research intervention caused their injury.<sup>255</sup> Participants in federally conducted research or international research face additional statutory barriers to recovery.<sup>256</sup> The net result is that “[u]nder the current negligence approach, only an extremely limited

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250. See, e.g., Pike, *supra* note 24, at 19.

251. See London, *supra* note 246, at 23.

252. See *id.* (arguing that continued reliance on the tort system as the sole means of compensation for research related injuries is morally indefensible because, among other reasons, it requires wrongful injury which is often either contrary to the facts of the research related injury or unable to be proven).

253. *Id.* at 26.

254. *Id.*

255. *Id.*

256. See *id.* at 29-38.

subset of injured research participants can bring a successful tort lawsuit: those who were injured in research that did not comply with federal regulations, when the injury arose due to the researchers fault, and in jurisdictions where research participants are not precluded from recovering by a signed informed consent document.”<sup>257</sup>

While those who are able to bring a successful suit under the current tort law framework have a clear claim to compensation in reparative justice, the scope of the reparative justice obligation is broader than what the current tort law framework allows. In order to match the scope of the obligation, the tort framework would need to undergo reforms, including removing some of the current barriers to suit in research related injury cases.<sup>258</sup> The tort system would then provide an adequate means of dealing with those cases where a research subject has been wrongfully injured due to some culpable act of a researcher, institution, or sponsor. The vast majority of research injuries where there is no culpable conduct cannot, however, be adequately accommodated under a tort law framework and should, instead, be subject to some form of no-fault compensation.<sup>259</sup>

In contrast to the limited scope of reparative justice, nonmaleficence provides a compelling justification for providing compensation for research related injuries in the majority of cases. Nonmaleficence, grounded in the relationship between sponsors, researchers, institutions, and subjects, is intertwined with the obligations already undertaken by sponsors, researchers, and institutions in other parts of the research enterprise. For example, the duty to minimize risks is incorporated into IRB review of research protocols, and the requirement that a protocol must be scientifically valid. There is no morally justified reason for the obligation to minimize risks to end with prospective physical or medical risks and not include the financial risks of research related injury. Furthermore, the relationship between the sponsors, institutions, researchers and subjects gives weight to a duty to act.<sup>260</sup> Finally, nonmaleficence

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257. *Id.* at 29.

258. For examples of current barriers see Pike, *supra* note 24, at 33.

259. See *id.* at 44; see also U.S. DEP'T OF HEALTH, EDUC., & WELFARE, *supra* note 27, at III-1; *Responsible Research: A Systems Approach to Protecting Research Participants*, INST. OF MED., <http://www.iom.edu/Reports/2002/Responsible-Research-A-Systems-Approach-to-Protecting-Research-Participants.aspx> (last visited May 5, 2014).

260. An analogy can be drawn here to tort law, where in the absence of some relationship between the person in peril and the potential rescuer, there is no duty to rescue. See W. PAGE KEETON ET AL., PROSSER AND KEETON ON TORTS, 375 (5th ed. 1984) (“Because of . . . reluctance to countenance ‘nonfeasance’ as a basis of liability, the law has persistently refused to impose on a stranger the moral obligation of common

creates a strong obligation to act because the ones who bear the duty are also those who are in a position to either mitigate or exacerbate harm and risk of harm to the participant during his or her enrollment in research.

In examining the principles underlying an obligation to provide compensation for research related injury, nonmaleficence and justice create complementary duties for sponsors, institutions, and researchers. In particular, sponsors, institutions, and researchers have a strong duty to compensate participants under a reparative justice model when they have caused the injury. Similarly, those entities have a well-founded duty to provide compensation under a theory of distributive and compensatory justice because they benefit financially and professionally from the participants' enrollment in research.<sup>261</sup> Although sponsors, institutions, and researchers generally have a vested interest in any given trial, assessing the total benefit of research to these actors is a complex task. After all, a trial may fail, giving no direct benefits to the sponsor, institution, or researcher involved, but providing information that may be useful to others involved in the research enterprise at some future time. At this point, it is sufficient to recognize that these actors have a definite stake in the continuation of research, but that the benefit to them may vary in degree based on many factors, including, but not limited to the type of actor and the outcome of the research.<sup>262</sup>

The duty of the general public, grounded in both distributive and compensatory justice, is difficult to compare with the duties held by sponsors, institutions, and researchers because the benefits accruing to each party are largely incommensurable.<sup>263</sup> Commercial sponsors of

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humanity to go to the aid of another human being who is in danger, even if the other is in danger of losing his life.”).

261. See Resnik, *supra* note 138, at 266, 269. Financial benefit is the more important metric here because this article is chiefly concerned with monetary compensation for economic harms, including, but not limited to, the cost of care and of lost wages due to disability. See also Childress, *supra* note 220.

262. *Compare Listing Revenues and Profits for Major Pharmaceutical Companies*, FORBES FORTUNE 500, available at <http://fortune.com/fortune500/2013/wal-mart-stores-inc-1> (last accessed Mar. 19, 2015), with Matthew Herper, *How Much Does Pharmaceutical Innovation Cost?*, FORBES (Aug. 11, 2013) available at <http://www.forbes.com/sites/matthewherper/2013/08/11/the-cost-of-inventing-a-new-drug-98-companies-ranked> (calculating estimated research and development costs per drug over the past ten years for one hundred pharmaceutical companies). In sum, the benefit that any individual sponsor, institution, or researcher reaps from research will be contingent upon the projects that they have invested in.

263. It is extremely difficult to objectively compare the value of a drug or intervention to the manufacturer (in terms of profits) with the value of that same intervention to an institution, which may benefit through

the device, drug, or intervention receive a large portion of the benefit generated, namely the profits. Public or non-profit sponsors may receive a lesser financial benefit, but they may gain other rewards from research, such as reputational gains and the satisfaction of seeing progress made in the area the sponsor chooses to focus on. Similarly, research institutions and researchers receive benefits from biomedical research—namely funding and prestige—which are less easily measured than pure financial benefits. These types of actors have a large stake in any given project, as well as an undeniable interest in seeing the continuation of the research enterprise. The public at large benefits immensely from the existence of the research enterprise as a whole, but public benefit is not necessarily contingent upon the success of any particular study.<sup>264</sup> As Alan Wertheimer has eloquently stated in response to Hans Jonas's famous claim that progress is optional, "one person's 'optional progress' is another person's life or body."<sup>265</sup> The research enterprise produces a vast social good because it transforms yesterday's experimental drugs, devices, and interventions into today's standard therapies.<sup>266</sup> It is difficult to compare the value of a drug to an individual whose life it saves with the value of that same drug to the company that reaps the profits. It can, nonetheless, be determined that the public as a whole receives great benefit from research and should therefore, under a theory of compensatory justice, bear some of the burden of compensation for research related injuries.

The benefits of the research enterprise are spread widely across a number of actors who have varying degrees of obligation to compensate the individuals who have been injured during the research process. In light of the different obligations created, a compensation system guided by the principles of nonmaleficence and justice should take into account the many beneficiaries of research, and spread the burden of compensation accordingly. Such a model should have the cost of compensation borne by all those with a stake in the research enterprise including sponsors (both private and public), institutions, researchers, and, of course, the public at large.

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growth and prestige, or with the benefit of the same intervention to an individual whose quality of life is improved.

264. Rid & Wendler, *supra* note 21, at 145. *See also* Childress, *supra* note 220.

265. ALAN WERTHEIMER, *RETHINKING THE ETHICS OF CLINICAL RESEARCH: WIDENING THE LENS* 12 (2010).

266. *See id.*

### III. USING ETHICAL JUSTIFICATIONS TO DEFINE “COMPENSABLE INJURY”

#### A. Causation

All justifications for compensation of research related injury incorporate a requirement of causation. A duty of risk-minimization based in nonmaleficence requires compensation only for those injuries that foreseeably arise as part of the research process.<sup>267</sup> The justification for this approach is that the duty bearers within the research enterprise cannot be held responsible for risks outside of those that they have an obligation to minimize.<sup>268</sup> This requires that compensation be limited to those injuries that are caused by the subject's participation in research.<sup>269</sup> Similarly, a duty based in distributive and compensatory justice requires compensation for those injuries occasioned by the research participant's decision to participate in biomedical research, thereby foregoing the standard of care.<sup>270</sup> It is this decision that produces the benefits of medical research and scientific progress that are received by both the research enterprise and society as a whole.<sup>271</sup> Injuries that can be traced back to that decision should be compensated as research related injuries. Finally, the duty of reparative justice requires compensation for those injuries that have been caused by the negligence or malfeasance of someone within the research enterprise.<sup>272</sup>

The path that causation must tread in these cases is analogous to that required by courts in evaluating claims of negligence.<sup>273</sup> As illustrated above, different international systems of compensation

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267. See, e.g., Joffe & Miller, *supra* note 21, at 36; see also U.S. DEP'T OF HEALTH, EDUC., & WELFARE, *supra* note 27, at 10 (noting the broad foreseeability of research related injuries and citing that as a reason that might bar recovery in tort).

268. See *supra* Part II.

269. This might also place policy based limits on what injuries caused by research should be compensable—for example, risks that are of the type research sponsors, researchers and institutions are well equipped to guard against might be outside of the scope of responsibility, for example, a car accident on the way to the research clinic. Limits of this type were once contained under the heading of proximate cause, but are more appropriately addressed as limitations on the scope of responsibility. See, e.g. RESTATEMENT (THIRD) OF TORTS: PHYS. & EMOT. HARM ch. 6, spec. note (2010).

270. See *supra* Part II.

271. See *supra* Part II.

272. See *supra* Part II.

273. See, e.g., H.L.A. HART & TONY HONORÉ, CAUSATION IN THE LAW 20 (2d ed. 1985).

require different proof of causation when it comes to research related injuries. In order to more clearly determine what it means for an injury to be caused by research, it is necessary to look at theories of causation more broadly and to examine causation in the research context. In particular, causation cannot be isolated from an analysis of whether participants received the appropriate standard of care. In so-called therapeutic research, it is often difficult to determine whether a patient-subject's worsening condition is the result of a research related injury or of the natural progression of the individual's underlying disease state.<sup>274</sup> These considerations must be incorporated into a comprehensive system for determining which injuries can justifiably be said to have been caused by the research.

### 1. A Theory of Causation

The concept of causation is deceptively difficult. Although the language that is used when discussing causation is both intuitive and intended to be interpreted by lay people, an analysis of causation as it is used in the law leads to complex questions about both the origin and the attribution of events. At this point, it is useful to draw upon the work of H.L.A. Hart and Tony Honore, who have undertaken a thorough examination of causation in the law.<sup>275</sup> Their analysis of causation aims to explicate what separates a cause from a mere condition of the occurrence of an event, and it also explores the conditions under which the determination that an event is the cause of another leads to an attribution of responsibility for the consequences of that event.

#### *a. Causes and Conditions*

Causes, as they are used in the legal or historical lexicon, must be distinguished from the causal concepts used by scientists and philosophers.<sup>276</sup> In general, lawyers are concerned with the attribution of responsibility for the consequences of an action.<sup>277</sup> Hart and Honore draw upon the work of Hume and Mill to conclude that for any given occurrence, a number of factors are necessary to produce the ultimate

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274. See Henry et al., *supra* note 115, at 5. (“[P]roving causation is problematic for research participants, many of whom suffer from underlying medical conditions that make it difficult to determine whether their alleged injury is the result of the experimental intervention or their disease.”).

275. See generally HART & HONORÉ, *supra* note 273.

276. *Id.* at 17-20.

277. *Id.* at 20. (“[T]he lawyer, the historian, and the plain man accept the doctrine that an event of a given kind may be produced by different causes. They are perfectly prepared to treat, for example, death, as caused by poisoning, sometimes by starvation, and sometimes by shooting . . . .”)

effect.<sup>278</sup> They therefore argue that “when we identify single events as causes it appears that we choose one element from such a set, although each of the members of the set is equally required for the production of the effect.”<sup>279</sup> A classic example is the case of determining the cause of a fire when a lighted match was dropped into a wastepaper basket. It is intuitive to say that the lighted match caused the fire, even though the presence of oxygen was also a necessary background condition.<sup>280</sup>

The natural question presented is, therefore, what separates an element that is considered to be a “cause” from other factors necessary to produce the effect?<sup>281</sup> One explanation is that a cause “is an interference in the natural course of events which *makes a difference* in the way these develop.”<sup>282</sup> This definition is particularly useful for “simple cases” where an individual produces “some desired effect by manipulation of an object in [the] environment.”<sup>283</sup>

One important feature of this approach is that it takes into account the normal background conditions in which a cause operates. It rests on a “presumption, normally fulfilled but rebuttable, that when we deliberately intervene in nature to bring about effects which in fact supervene, no other explanation of their occurrence is to be found.”<sup>284</sup> Normal conditions are those that are present both in the ordinary functioning of the item or process in question, and in the case of an accident or mishap.<sup>285</sup> They are therefore ruled out as a

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278. *Id.* at 17.

279. *Id.*

280. The Restatement (Third) of Torts largely adopts Hart and Honoré’s view with the exception that it does not distinguish between causes and conditions, but rather considers all conditions necessary for the occurrence of an event to be “causes.” Causes are then divided into “relevant causes” (those brought about by tortious conduct) and “background causes.” Tortious conduct must only be a cause of harm in order for liability to follow. RESTATEMENT (THIRD) OF TORTS: PHYS. & EMOT. HARM § 26 cmt. (d) & Reporter’s Note (2010). Because the language used in the restatement may prove confusing in a non-legal context where there is often no tortious conduct, this article relies upon the more traditional language which distinguishes causes of an event from conditions for its occurrence.

281. HART & HONORÉ, *supra* note 273, at 17.

282. *Id.* at 29. This should be distinguished from the “substantial factor” test, which has been soundly rejected by RESTATEMENT (THIRD) OF TORTS: PHYS. & EMOT. HARM § 26 cmt. (j) (2010), and regarded as a further exploration of the concept of factual causation.

283. HART & HONORÉ, *supra* note 273, at 29.

284. *Id.* at 32.

285. *Id.* at 34.



cause of any particular accident.<sup>286</sup> “[N]ormal conditions (and hence in causal inquiries mere conditions) are those conditions which are present as part of the usual state or mode of operation of the thing under inquiry.”<sup>287</sup> For example, when considering what caused a train accident, a bent rail is likely to be considered a cause, because it, rather than the speed and weight of the train operating as usual, made the difference between the train’s normal functioning and its derailment.<sup>288</sup> This is the case even though the crash would not have occurred as it did if the train were not traveling at that speed or if it did not have the same weight.<sup>289</sup>

Causal definition in this manner is particularly useful in the research context. To begin with, it supports the proposition that participation in research must be a cause in fact, or *sine qua non*, of a research related injury.<sup>290</sup> It also tells us, however, that the inquiry must not stop there. To say that an injury would not have occurred but for the subject’s participation in research only identifies research as one of the background conditions that was necessary for the injury to occur. It does not pluck it out from among those conditions and identify it as a cause of the injury.<sup>291</sup> This definition, without more, would not rule out compensation for injuries that, for example, occur due to traffic accidents on the way to the research clinic.<sup>292</sup> In order to identify research participation as the cause of the injury, it is therefore necessary to determine what research activity has caused a deviation from the normal conditions that otherwise would have prevailed.

This definition excludes the natural progression of a patient/participant’s illness as a cause of a research related injury if the illness would have progressed regardless of the individual’s participation in research. For example, imagine the case of an individual with advanced cancer, for whom all standard treatments have failed. This individual’s prognosis is poor, and death is likely to occur. Because death is the expected outcome for this participant, due to the natural progression of his or her disease, failure of a clinical

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286. *Id.*

287. *Id.* at 35.

288. *Id.* at 34.

289. *See id.*

290. *See id.* at 17.

291. *See, e.g., id.* at 17, 34.

292. Such injuries should be ruled out because, in those cases, there is another primary duty bearer, namely the motorist who injured the research subject, and also because they are not the types of injury that a compensation scheme is designed to protect against. *See supra* note 269 on scope of liability.

trial intervention to avert that outcome is not a change in the normal operating conditions that will make a difference in the way those conditions develop. The search for a cause, as distinguished from a mere condition for the occurrence of an injury, should also guide the search for an explanation for any given injury.

What counts as a normal condition for a particular occurrence may often be the product of human habit, custom, or convention.<sup>293</sup> This observation is of particular importance in the medical context because, with the knowledge that some conditions are harmful in the absence of human intervention and are commonly ameliorated with appropriate medical attention, it becomes the normal state of affairs to intervene, and the lack of intervention is therefore a deviation from the normal course of events.<sup>294</sup> An example is helpful to understand how this principle operates in practice. Imagine that Ms. Smith has been diagnosed with pneumonia. In the ordinary course of events, it is known that prompt treatment with antibiotics is generally curative, and that in the absence of treatment, the pneumonia may become significantly worse.<sup>295</sup> In this case, it could be said that the failure to treat Ms. Smith's pneumonia was the cause of the advancement of her disease and her ultimate death.

*b. Causes and Human Action*

In identifying a cause of an event, special importance is given to voluntary human action. It "is often regarded both as a limit [on how far back we trace the chain of causation] and also as still a cause even though other later abnormal occurrences have provisionally been recognized as causes."<sup>296</sup> An ordinary causal inquiry, in which we are seeking to explain an occurrence, will not ordinarily be traced "*through* a deliberate act."<sup>297</sup> Abnormal consequences that follow a deliberate act are also likely to be regarded as mere means by which the act reaches its natural end.<sup>298</sup> A deliberate human act is therefore a natural boundary for the causal inquiry. We do not trace the path of a later event back through it, and we pass through intermediate causes of other kinds on our way to it.<sup>299</sup>

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293. HART & HONORÉ, *supra* note 273, at 37.

294. *See, e.g., id.*

295. *How is Pneumonia Treated?*, NAT'L HEART, LUNG & BLOOD INST., <http://www.nhlbi.nih.gov/health/health-topics/topics/pnu/treatment.html> (last visited Aug. 11, 2014).

296. HART & HONORÉ, *supra* note 273, at 42.

297. *Id.* at 43.

298. *See id.*

299. *See id.* at 44.

Our inquiry thus far should lead to the conclusion that a cause will differ from other necessary circumstances for the occurrence of a later event because it will be an abnormal condition, and it will often be brought about by a deliberate human action. A cause, once identified, should also be unproblematically connected to the consequences or effect it produced.<sup>300</sup> This means that it should fit within the broad generalizations about what types of action produce what types of effects, and it should also fit within the framework of past cases.<sup>301</sup>

The causal inquiry we seek to enter into in the research related injury context has both explanatory and attributive aspects.<sup>302</sup> In asking what caused a particular research injury, an explanation is sought for the origin of the injury, and the question is asked as to who, if anyone, should be held responsible for the damage. In linking a consequence to its cause, we encounter a number of intervening factors and conditions, some of “which are not only subsequent to, but independent of the initiating action or event.”<sup>303</sup> Imagine, for example, a participant who is sickened by the administration of the trial medication and is likely to die, but before the drug can have that effect, an old enemy, not knowing this is the case, stabs him to death. In assessing these intermediate factors, the mere background “conditions in or on which the cause operates” must be distinguished from those factors that may break the chain of causation.<sup>304</sup> Conditions are often separated from intervening causes by an analogy with the case of simple actions. In the usual case, a voluntary human action, which follows the initial “cause,” will break the proverbial causal chain. It is an intervention through which the cause is not traced.<sup>305</sup> In the example above, the administration of the trial drug could be said to have made the participant ill, but it was not the cause of his death; rather, the causal link was broken by the deliberate action of a third party. This case is contrasted with “actions which in any of a variety of different ways are less than fully voluntary,” and which “are assimilated to the means by which or the circumstances in which the earlier action brings about the

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300. *See id.* at 46.

301. *Id.* at 46-47.

302. *See id.* at 73.

303. *Id.* at 72.

304. *Id.*

305. *Id.* at 75 (explaining that this rule does not hold “where an opportunity commonly exploited for harmful action is negligently provided, or one person intentionally provides another with the means, the opportunity, or a certain type of reason for wrongdoing.”).

consequences.”<sup>306</sup> Similarly, the causal chain is broken by the occurrence of coincidences, so long as the coincidence was not contrived or intended by the initial actor (*i.e.* if our unfortunate research subject was killed by a falling tree branch rather than another person).<sup>307</sup> A cause will not be broken, however, by an abnormal state of the thing acted upon at the time that the act occurs. For example, if an individual (A) hits another (B), and it turns out that B had the proverbial “eggshell skull” and is killed by the blow, it would be said that A has caused B’s death even though B was unusually susceptible to harm and an ordinary person without that condition would not have been killed by a blow of the type that A delivered. Such a preexisting condition is merely “part of the circumstances in which the cause ‘operates.’”<sup>308</sup>

In seeking to explain the cause of an injury that occurs during research, it is necessary to trace the chain of events leading up to an injury back to the point where an abnormal occurrence disturbed what would otherwise have been the normal order of things. Voluntary human action is a particularly salient disturbance because we generally operate on the premise that voluntary conduct has the potential to alter the world in which it operates. Therefore, in tracing back the causal chain leading to an injury in the research setting, special attention should be paid to whether a human intervention (such as the taking of blood, administration of a novel drug, or performance of a medical procedure) is included in the chain of causation. Application of Hart and Honoré’s analysis to the research context also counsels that biological differences in research subjects that may make them more or less susceptible to injury should not be weighed in determining whether research participation truly was the cause of the injury.<sup>309</sup> The relationship between human action and causation does not counsel that all injuries following a research intervention are research related, but rather provides a useful guidepost for the causal question.

A second and related question will be whether this human intervention was performed for the purpose of furthering the aims of

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306. *Id.*

307. *Id.* at 78 (“We speak of a coincidence whenever the conjunction of two or more events in certain spatial or temporal relations (1) is very unlikely by ordinary standards and (2) is for some reason significant or important, provided (3) that they occur without human contrivance and (4) are independent of each other.”).

308. *Id.* at 80.

309. Of course, such considerations may need to be taken into account when determining whether certain potential participants should be excluded from research participation on the grounds of increased risk. See Dave Wendler, *When Should “Riskier” Subjects Be Excluded From Research Participation?*, 8 KENNEDY INST. ETHICS J. 307, 307 (1998).

research, or whether it was part of ordinary or concomitant medical care. This is addressed below in the context of the relationship between causation and the standard of care. It is not a causal inquiry in and of itself, but rather a baseline determination of whether the event that caused the injury was itself research related. By following this two-step process, the inquirer first determines whether an intervention was a cause of an injury, and next determines whether that intervention was research related.

*c. Causes and Principles of Policy*<sup>310</sup>

What is described as a cause “may have features which vary from context to context,” there may be “different types of causal inquiry,” and “there may not be a single concept of causation but rather a cluster of related concepts.”<sup>311</sup> Hart and Honoré have noted that there is an insistence in the modern critiques of the concept of causation that, “where the existence or the extent of liability for the violation of statute is in issue, a range of problems, which appear insoluble if considered in causal terms are relatively easily solved if viewed as questions concerning the scope or purpose of the statute, or the nature of the interests it was designed to protect.”<sup>312</sup> While Hart and Honoré do not endorse the modern critique in its entirety, they do acknowledge that the concept of policy limitations on causation has a proper place in an analysis of causation in the law. Limitations on causation may therefore be created not only by legal principles of causation, but also by “special principles of policy.”<sup>313</sup>

Such principles of policy are often introduced by way of analysis of foreseeability and risk. These concepts are balanced somewhat precariously on the border between truly causal questions and limitations on causation that are set as a matter of policy.<sup>314</sup> The foreseeability and risk doctrines aim to address the proper scope of the causal inquiry and provide a formula for determining when attribution of responsibility for an event is appropriate. Foreseeability

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310. Hart and Honoré preceded the Restatement (Third) of Torts in identifying proximate cause not as a type of cause, but rather as a principle of policy more appropriately addressed (as it is in the latest edition of the restatement) as dealing with the “scope of liability.” See RESTATEMENT (THIRD) OF TORTS: PHYS. & EMOT. HARM § 26 cmt. (a) & Reporter’s Note (2010).

311. HART & HONORÉ, *supra* note 273, at 19.

312. *Id.* at 102.

313. *Id.* at 93.

314. *Id.* (“A legal system may mark more or less strongly and in various ways the distinction between the limits on liability imposed by principles of causation and those imposed by special principles of policy[.]”).

may either limit or expand the scope of the causal inquiry.<sup>315</sup> In its limiting form, it holds that “only foreseeable harm is recoverable,” which serves to remove responsibility from the defendant for effects of his conduct that would not be predictable to the ordinary man at the time of its undertaking.<sup>316</sup> In its expansive form, foreseeability requires that all foreseeable harm, for which the defendant’s act was a necessary condition, be recoverable.<sup>317</sup> In practice, the concept of foreseeability has not been uniformly applied, and it often fails to adequately address questions where both an explanation and an attribution of cause are sought.<sup>318</sup> Risk theory, by contrast, asks who should bear the risk of a particular injury.<sup>319</sup> That determination is based in policy, and the answer may vary depending on the justification put forth. Risk theory, like foreseeability, both extends and restricts the attribution of consequences; however, unlike foreseeability, risk theory does so by restricting liability to “those types of harm the chance or risk of which formed *the* reason or a reason for the imposition of liability.”<sup>320</sup>

Although foreseeability seems like a logical fit for the research context with its focus on prospective risk mitigation, risk theory is particularly applicable to the problem of compensation for research related injuries. The justification for requiring compensation in these cases is often not rooted in negligence, but in a considered determination of who, all things considered, ought to bear the risk of injury.<sup>321</sup> It flows from that determination that recovery should be limited to those types of harm that are justified by that allocation determination. Within that limitation, however, a risk theory analysis would be incomplete without reference to causal concepts.<sup>322</sup> Risk theory is most useful here to set an outer limit on the causal inquiry so that compensation is provided when the injury is caused by research and when it is within the risks that led to the imposition of a compensation obligation in the first place.<sup>323</sup> Such a limitation serves

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315. *See id.* at 258. The foreseeability inquiry can also be framed as one of proximate cause or scope of liability. *See* RESTATEMENT (THIRD) OF TORTS: PHYS. & EMOT. HARM ch. 6, spec. note (2010).

316. *See id.* at 263, 275.

317. *Id.* at 275.

318. *See id.* at 284.

319. *Id.* at 285.

320. *Id.* at 86.

321. *See supra* Part II.

322. HART & HONORÉ, *supra* note 273, at 285.

323. This can also be thought about in terms of defining the scope of liability. *See* RESTATEMENT (THIRD) OF TORTS: PHYS. & EMOT. HARM ch. 6 spec. note (2010).

the purpose of ensuring that the law as implemented is in line with the justifications for imposing a compensation requirement in the absence of culpable conduct.

Finally, it should be noted that causation, as a concept in the law, cannot be entirely divorced from notions associated with moral responsibility. In general, “to say that someone is responsible for some harm means that in accordance with legal rules or moral principles it is at least permissible, if not mandatory, to blame or punish or exact compensation from him.”<sup>324</sup> It is not true however that such a correlation is present in all cases. The law is well within its purview to draw a line around illegal conduct that is different from the common morality.<sup>325</sup> It is therefore the case that moral blame is neither necessary nor sufficient for legal responsibility.<sup>326</sup> In some cases, however, it is desirable to draft a law that best matches the ethical obligations of the regulated parties so that the values embodied in the law mirror those of the common morality.<sup>327</sup> This is particularly the case in the regulation of biomedical research, which has its own field dedicated to the analysis of what constitutes the proper ethical conduct of research activities.<sup>328</sup> In part due to the evolving understanding of the ethics of clinical research, the law has attempted to mirror the ethical obligations of the parties involved in order to promote a balance between protecting the interests of research participants and allowing for the advancement of medical science.<sup>329</sup>

Policy considerations can and should guide the development of the scope of responsibility within which causal concepts operate in compensation systems for research related injury.<sup>330</sup> Experience demonstrates that when cause is defined too broadly or not limited in scope, it can have a damaging effect on the research enterprise.<sup>331</sup> This

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324. HART & HONORÉ, *supra* note 273, at 65.

325. *See, e.g.*, Meir Dan-Cohen, *Decision Rules and Conduct Rules: On Acoustic Separation in Criminal Law*, 97 HARV. L. REV. 625, 650-51 (1984).

326. HART & HONORÉ, *supra* note 273, at 67.

327. *See, e.g., id.* at 66. *See also* Dan-Cohen, *supra* note 325, at 650-51.

328. *See* Emanuel et al., *supra* note 156, at 2701.

329. *See, e.g.*, London, *supra* note 246. *See generally* Cass R. Sunstein, *On the Expressive Function of Law*, 144 U. PA. L. REV. 2021 (1996) (discussing the law’s tendency to not only reflect but also fortify social norms).

330. In the past, this idea has been associated with the concept of proximate cause. It is akin to scope of liability as laid out in the Restatement (Third) of Torts, *supra* note 310.

331. *See* Kripa Mahalingam, *Critical Condition*, OUTLOOK BUSINESS (Mar. 1, 2014), [http://business.outlookindia.com/article\\_v3.aspx?artid=289527](http://business.outlookindia.com/article_v3.aspx?artid=289527).

was the case when India first introduced its new requirements for compensation of research related injuries, and it resulted in numerous companies either pausing or withdrawing from research in India.<sup>332</sup> The scope of responsibility should not be defined so broadly that it prevents the biomedical research enterprise from performing its core function, namely the development of novel therapies and devices for treatment of medical conditions. There is a delicate balance to be struck between the moral claims of injured research subjects and the social benefit produced by the continuation of the research enterprise. It is therefore advisable to use policy as a tool to limit the reach of causation when necessary to protect countervailing social concerns.

## 2. A Theory of Causation for Research Related Injuries: The Positive Case

In light of the above discussion, it is possible to put forth a positive account of what it means for an injury to have been caused by research. To begin with the most basic elements of causation, it must first be the case that the subject's participation in research is a cause in fact of the injury—in other words, that the injury would not have occurred but for the decision to enter into research. Next, a research intervention must create a condition that differs from the normal course of events, and that condition must lead (sometimes through a series of events) to the injury. This definition includes injuries due to administration of the study intervention and injuries incurred due to performance of medical procedures that are necessary for research, but are not clinically indicated.<sup>333</sup>

Injuries that are due to the natural progression of the participant's illness and those injuries that result from the participant's deviation from the research protocol are excluded

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332. *Id.*

333. It should be noted that this proposed definition tracks closely with that provided by HEW SECY'S TASK FORCE ON THE COMP. OF INJURED RESEARCH SUBJECTS, U.S. DEP'T. OF HEALTH, EDUC. & WELFARE, REPORT OF THE TASK FORCE II-2 (1977) [hereinafter SECY'S TASK FORCE], which stated that human subjects who suffer physical, psychological, or social injury in the course of research conducted or supported by the PHS should be compensated if (1) the injury is proximately caused by such research, and (2) the injury on balance exceeds that reasonably associated with such illness from which the subject may be suffering, as well as with treatment usually associated with such illness at the time the subject began participation in the research. The definition proposed here is different because it relies on a more robust theory of causation that is tailored to the research context and limits the types of injuries considered (see *infra*). These changes are supported by the experience of the international community in confronting this topic (see *supra* Part I.A) and by the fact that the locus of responsibility under this proposal is not being placed upon the federal government, as the 1977 task force recommended.



because in those cases the research intervention cannot be identified as a *cause* among the many conditions that were necessary for the injury to occur.<sup>334</sup> When a research intervention is one of multiple causes of an injury, reduction in the amount of compensation may be appropriate.<sup>335</sup> The reduction in compensation should be proportionate to the contribution of the various causes (if that could be determined) and it should also reflect the fact that not all of the harm can be said to have been caused by research related interventions. Risk theory may provide some guidance in borderline cases because it allows consideration of which party ought to bear the risk of injury to come into the decision-making process when deciding whether compensation is owed. In practice, this should mean that in borderline cases, the evidence should be interpreted leniently in favor of the injured subject.<sup>336</sup>

### 3. Intersection of Causation with the Standard of Care: The Negative Case

A second question that arises when attempting to determine whether an individual has suffered a research related injury is in what cases an omission can be said to be the cause of a research related injury. An omission in this case is best defined as the failure to provide medically indicated treatment for the participant-subject's underlying disease or condition. A clinical trial operates against the background of the *de facto* standard of care in the host nation.<sup>337</sup> The *de facto* standard of care is one in "which the standards of medical practice for a community are set by the actual medical practices of that community."<sup>338</sup> In general, when an individual enters a clinical

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334. This is under the theory of contributory negligence. True, the research participation creates an opportunity for the injury to occur, but it is the participant's negligent conduct that causes the injury, whereas if the participant had followed the protocol, the injury would not have occurred. There may be an exception to this principle available if the participant can demonstrate that the burden of compliance was unreasonably high, but this is not likely because the participant should have been able to judge, when entering the research, whether compliance would be feasible. All responsibility in these cases cannot and should not be placed on individuals other than the patient.

335. See HART & HONORÉ, *supra* note 273, at 180.

336. Henry et al., *supra* note 115, at 10-11. This is similar to giving the participants the benefit of the doubt when determining whether an injury was research related.

337. See Alex John London, *The Ambiguity and the Exigency: Clarifying "Standard of Care" Arguments in International Research*, 25 J. MED. & Phil. 379, 382 (2000) (defining the *de facto* standard of care as the local standard of actual medical practice).

338. *Id.* London also illustrates that this can be distinguished from the "*de jure*" standard of care which is set not by actual practice, but "by the

trial, he or she faces a choice between trial participation and seeking standard of care treatment in the community.<sup>339</sup> In practice, this choice may be constrained on an individual basis by a number of factors including the availability of medical care in the community, the individual's financial resources, and the success that the individual has had with other treatments, if such treatments have previously been tried. It is intuitive to think that an individual, on account of his or her greater financial resources, may have access to a better standard of care than is generally available locally, but for the majority of research participants this will not be the case.

If the individual chooses to participate in research, he or she might receive the study intervention or be placed in the control arm. The control arm is the standard against which the new intervention is tested.<sup>340</sup> There is currently a robust debate as to what standard of care must be provided in the control arm of international clinical trials, and whether it is ever acceptable to provide less than the best available standard of care.<sup>341</sup> It has been convincingly argued, however, that it may be appropriate for a study to test an intervention against less than the best available standard of care where four criteria are met: (1) scientific necessity, (2) host community relevance, (3) sufficient host community benefit, and (4) subject and host community non-maleficence.<sup>342</sup> Under these criteria, there is substantial room for difference between research projects as to what may ethically be used as a control.<sup>343</sup> The question then

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judgment of experts in the medical community as to which diagnostic and therapeutic practices have proven most effective against the illness in question." *Id.* at 384.

339. See, e.g., David Wendler et al., *The Standard of Care Debate: Can Research in Developing Countries Be Both Ethical and Responsive to Those Countries' Health Needs?*, 94 AM. J. PUB. HEALTH 923, 924 (2004) (describing short course AZT trials and the decision faced by participants of receiving the trial intervention or a placebo, which was consistent with the care that would have been available in the community outside of the research setting).

340. See *id.*

341. See London, *supra* note 337. See also Wendler et al., *supra* note 339.

342. Wendler et al., *supra* note 339, at 927. The authors define those terms as follows: "(1) scientific necessity: investigators must use less than the worldwide best methods to answer the scientific question posed by the trial; (2) relevance for the host community: answering the scientific question posed by the trial will help address an important health need of the host community; (3) sufficient host community benefit: the trial will produce a fair level of benefit for the host community; and (4) subject and host community nonmaleficence: subjects and the host community will not be made prospectively worse off than they would be in the absence of the trial."

343. See *id.*

presented by the standard of care debate is under what circumstances injuries resulting from randomization to the control arm of a clinical trial can be counted as an injury that is caused by research participation.

As was noted above, something is the cause of a later event where it is both a necessary condition for the occurrence of that event and it reflects a change or aberration from the conditions that would have been present under normal circumstances.<sup>344</sup> Conduct that causes injury may be described either as an act or an omission.<sup>345</sup> As Hart and Honoré have noted, “if there is a legal duty to do an act, and the subject has not done it, the legally relevant description will be in terms of an omission to perform the act in question.”<sup>346</sup> The same framework can be applied to the ethical obligations held by researchers, sponsors, and institutions. In general, researchers have a positive ethical obligation to provide the ethically justified standard of care treatment to their research subjects.<sup>347</sup> As noted above, this principle is softened when there are good reasons to believe that it is necessary to use either a placebo control or the local standard of care in order to produce a valid and valuable scientific result.<sup>348</sup> When the conditions for a permissible deviation from the best available standard of care are met, failure to provide the best available standard of care should not constitute a research related injury.

Under this framework, the local *de facto* standard of care provides a sharp lower boundary for the inclusion of failure to provide standard care in the definition of a compensable research related injury. Even if the control arm may permissibly use something less than the local standard of care (*e.g.*, a placebo), research participants who choose to forego the (higher) local *de facto* standard of care in order to participate in the clinical trial and suffer an injury because of that decision may causally attribute that injury to the failure to provide appropriate medical care that would otherwise have been available.<sup>349</sup> Under this framework, the failure to provide the *de facto*

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344. See *supra* Part III.A.

345. HART & HONORÉ, *supra* note 273, at 138.

346. *Id.* at 139.

347. See, *e.g.*, Wendler et al., *supra* note 339, at 927. See also BEAUCHAMP & CHILDRESS, *supra* note 151, at 153.

348. See Wendler et al., *supra* note 339, at 927.

349. It is an open question at this point whether the *de facto* local standard of care or the *de jure* local standard of care is the most appropriate baseline measure. The important point to be made, however, remains the same: failure to provide care where there is an obligation to provide that care may be counted as a cause of an injury that flows from the lack of care and would not have occurred in its absence. See, *e.g.*, London, *supra* note 337. See also BEAUCHAMP & CHILDRESS, *supra* note 151, at 153.

local standard of care is the cause (by omission) of any ill effects that would not have occurred but for the decision of the participant to forego standard of care treatment.<sup>350</sup>

A duty to pay compensation for injuries due to failure to provide the ethically appropriate (as opposed to the local *de facto*) standard of care is supported by the principle of nonmaleficence and its requirement of risk minimization.<sup>351</sup> Nonmaleficence requires research sponsors, institutions, and researchers to “strive to minimize, consistent with the scientific aims of their research, the risks and burdens their experimental procedures impose.”<sup>352</sup> Part of the obligation of risk minimization is the requirement that the study intervention be tested against the best available standard of care unless there are ethically and scientifically valid reasons for downward deviation.<sup>353</sup> An injury caused by the failure to provide the appropriate standard of care is one caused by an omission in the presence of a duty.<sup>354</sup> It should therefore be considered a compensable research related injury.

As Hart and Honoré have noted, “[a] legal system may mark more or less strongly and in various ways the distinction between the limits on liability imposed by principles of causation and those imposed by special principles of policy.”<sup>355</sup> As a matter of public policy, many countries may have valid reasons to limit compensable injuries due to failure to provide the standard of care to those where the local *de facto* standard of care has not been provided. This policy is supported by the principle of compensatory and distributive justice because it rewards the choice to participate in research and the decision, implicit in that choice, to forego standard of care treatment in the community.<sup>356</sup> It is this choice that produces societal benefit in the form of medical progress.<sup>357</sup> A decision to participate in research is valuable because results, whether or not they support the use of the studied intervention, provide medical knowledge that is useful for future experimentation.<sup>358</sup> It is ethically desirable, then, to distribute the burdens of research related injury as broadly as the benefits. In

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350. See HART & HONORÉ, *supra* note 273, at 138 (defining a cause by omission).

351. See *supra* Part II.

352. See Joffe & Miller, *supra* note 21, at 36.

353. See Wendler et al., *supra* note 339, at 927.

354. HART & HONORÉ, *supra* note 273, at 139.

355. *Id.*

356. See *supra* Part II.

357. *Id.*

358. Henry et al., *supra* note 115, at 7.

this way, what might be an unbearable burden for one person is a relatively light burden when spread more broadly.

The precise nexus of causation with the standard of care, therefore, depends on a number of factors: (1) the care that would be available to participants outside of the research setting; (2) the standard of care that researchers are ethically obligated to provide; (3) the justification supporting the compensation requirement; and (4) in light of the preceding three factors, was the injury caused by the failure to provide a particular standard of care when that same standard of care was owed? The standard of care that is owed will vary depending on the precise conditions in which a clinical trial is situated, but it is important to make clear that the procedure for distinguishing compensable research related injuries from injuries incident to provision of medical care can be applied in a uniform manner.<sup>359</sup>

### *B. Type*

The second element of a well-regulated injury is that of type. Type refers to the distinction between medical<sup>360</sup> injuries and other types of intangible harm. Intangible harms have been recognized as an important subset of risks to which research participants may be exposed.<sup>361</sup> The Declaration of Helsinki requires that researchers recognize and guard against risks to the “life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.”<sup>362</sup> The Belmont Report’s requirement that ethical research have “respect for persons” may also support recognition of some types of intangible harm.<sup>363</sup> Others have argued that such intangible harms might include:

[N]ot only emotional distress, but also lost opportunity costs, destruction of trust and confidence in the research process, clinical trial abandonment, affront to dignitary interests, breach of confidentiality, invasion of privacy, loss of meaningful choice about use of one’s body as an experimental object, participation

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359. RESTATEMENT (THIRD) OF TORTS: PHYS. & EMOT. HARM § 26, cmt. n (2010). *Lost Opportunity or Lost Chance as Harm* may provide some valuable insight into the evaluation of damages where it is difficult to determine what the research participant’s precise medical course would have been if the research participant had either opted not to enroll in research or been randomized differently.

360. Documented mental health injuries (such as the onset of post-traumatic stress disorder) requiring further medical treatment should be considered “tangible” injuries for purposes of compensation.

361. See Saver, *supra* note 173, at 941,

362. WMA DECLARATION OF HELSINKI, *supra* note 35.

363. Saver, *supra* note 173, at 952.

in a study that fails to disseminate trial data in order to advance medical knowledge, and frustrated access to perceived cutting-edge therapy.<sup>364</sup>

The question presented is, therefore, whether both tangible and intangible injuries should be compensated in light of the ethical principles that justify the creation of a compensation requirement.

The principle of nonmaleficence is implemented through the requirement for risk minimization. Risk minimization is not without its limits, and may be constrained by considerations of cost, participant autonomy, and scientific integrity.<sup>365</sup> In particular, researchers' duty to minimize risks is constrained by the ability to accurately predict the harms that might arise as a consequence of a particular clinical trial. This should include the elimination of foreseeable intangible harms such as dignitary harms flowing from the failure to obtain fully informed consent. A duty to minimize dignitary and intangible harms does not necessarily imply that those harms should also be compensable.

Intangible harms that do not flow from some form of wrongful conduct are likely to be unforeseeable and difficult to prove within any compensation framework. For example, Brazil's regulations on research related injury allow for compensation in cases of spiritual injury.<sup>366</sup> What will be found to be injurious to the spirit is, by its nature, a deeply subjective inquiry that is not easily predictable without an in-depth screening of potential research participants' spiritual beliefs. Nonmaleficence therefore provides weak justification for the provision of compensation as a remedy for these types of harms. In addition to the weak normative justification, it is unclear that compensation would provide an appropriate remedy for the type of harm suffered in these cases because there are often no economic damages. In the absence of wrongdoing, punitive damages are inappropriate.

Compensatory and distributive justice, by contrast, seek to reward the decision of individuals to participate in research rather than seek standard of care treatment. It may therefore be the case that distributive and compensatory justice require compensation for all injuries caused by the decision to participate in research without regard to type.<sup>367</sup> This may be limited in application, however,

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364. *Id.* at 946.

365. *See* Joffe & Miller, *supra* note 21, at 36.

366. *See* NAT'L HEALTH COUNCIL, ON RESEARCH INVOLVING HUMAN SUBJECTS, Res. No. 196/96 (1987).

367. *See, e.g.,* U.S. DEP'T OF HEALTH, EDUC., & WELFARE, *supra* note 27, at II-2 (stating that "[h]uman subjects who suffer physical ~ psychological ~ or social injury in the course of research conducted or supported by the PHS should be compensated . . .").

because of practical problems of proof with respect to intangible harms in the absence of clear evidence of wrongdoing.<sup>368</sup> In particular, claims of intangible harm are not subject to objective proof, and they are not of the sort where the monetary cost of compensation could be easily predicted.<sup>369</sup>

Compensation systems in other countries and the tort framework in the United States have dealt with this type of uncertainty by requiring that an intangible harm be paired with a physical injury or proximity to a physical injury in order to be compensable.<sup>370</sup> It may be reasonable to define a certain subset of intangible harms that are particularly likely to flow from research participation as opposed to clinical care and to limit compensation to those defined circumstances in order to mitigate problems with burdens of proof.<sup>371</sup>

Finally, reparative justice aims to compensate an individual for all harms flowing from the wrongful conduct of another. Many of the most salient intangible harms are those that stem from some form of wrongful conduct such as the failure to ensure informed consent or abuse of the power imbalance inherent in the investigator-subject relationship.<sup>372</sup> Reparative justice seeks to put the harmed individual in as good a position as if the wrong in question had never happened. The principle of reparative justice therefore counsels that all types of injury should be compensable, subject to some of the same possible limitations on proof that arise in the context of distributive and compensatory justice. In cases like these, an alternative remedy may be appropriate such as nominal compensation and recognition of the harm done.<sup>373</sup>

In light of the foregoing discussion, the principles requiring compensation may support inclusion of intangible harms, but

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368. *See Canterbury v. Spence*, 464 F.2d 772, 787 (D.C. Cir. 1972) (holding that a physician seeking informed consent “cannot know with complete exactitude what the patient would consider important to his decision, but on the basis of his medical training and experience he can sense how the average, reasonable patient expectably would react.”).

369. Indeed, many no-fault compensation systems in the United States have awarded a flat sum for intangible harms, such as pain and suffering, because the difficulty of trying to evaluate individual circumstances would have threatened to overwhelm the claims process. *See, e.g.*, KENNETH R. FEINBERG, WHO GETS WHAT: FAIR COMPENSATION AFTER TRAGEDY AND FINANCIAL UPHEAVAL 104 (2012).

370. *See, e.g.*, New Zealand Accident Compensation Act 2001, SR 49/2001. *See also* Saver, *supra* note 173, at 948.

371. *See, e.g.*, FEINBERG, *supra* note 369, at 104 (describing Hokie Memorial Fund Plan, which based compensation for pain and suffering on length of hospital stay, rather than an individual analysis).

372. *See* Saver, *supra* note 361, at 990.

373. *See id.* at 999.

practical and evidentiary concerns may justify limiting the universe of compensable injuries to only those where there is medical harm. Often care for the medical harms that may result from a research injury might mitigate intangible harms such as feelings of abandonment which could otherwise have flowed from the same event.<sup>374</sup> In such cases, treatment and compensation for physical injuries is sufficient to ameliorate any harm done. Where there is an intangible harm that is attendant to a physical harm, additional compensation may be appropriate. And where there is an intangible harm stemming from wrongful conduct, some form of redress is appropriate, although compensation may not be the best remedy for the harm done.<sup>375</sup>

### *C. Degree*

Degree (or “magnitude”) of harm refers to the severity of the injury suffered. When analyzing risks, researchers, and IRBs are well advised to consider what procedures or interventions would be used in standard of care treatment, and to exclude those from the calculation of the risk that the research poses.<sup>376</sup> Similarly, when determining what degree of harm should be considered compensable, the level of risk inherent in the research project and the level of discomfort associated with standard care should be considered.<sup>377</sup> In agreeing to enroll in a trial, research participants consent to some degree of discomfort that is inevitable even if everything goes as planned.<sup>378</sup> Degree can be used to separate those injuries where treatment is sufficient to fulfill the duty owed to the research subject from those injuries where financial compensation is also warranted.

Nonmaleficence does not require that research be risk-free; rather, it merely requires that risks be minimized consistent with the scientific aims of the study.<sup>379</sup> Requiring monetary compensation for all injuries, regardless of degree, would overstate the obligation owed

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374. *See id.* at 1002.

375. Richard Saver has suggested a number of remedies, including a judicial forum akin to that provided for civil rights litigation. *See id.* at 992.

376. *Id.* at 955-956.

377. *See* U.S. DEP’T OF HEALTH, EDUC., AND WELFARE, *supra* note 27, at II-2 (stating that research injuries should be compensated if “[t]he injury on balance exceeds that reasonably associated with such illness from which the subject may be suffering, as well as with treatment usually associated with such illness at the time the subject began participation in the research.”).

378. For example, participants in a malaria vaccine challenge study should know (if consent was properly informed) that they might get malaria. *See generally* 45 C.F.R. § 46 (2009) (setting forth requirements for informed consent).

379. Joffe & Miller, *supra* note 21, at 36.



on the part of the research enterprise.<sup>380</sup> Other protections, such as IRB review and informed consent, ensure that participants are aware of the burdens of research participation, and participants may be compensated for those burdens in the form of payment for participation or provision of ancillary medical care.<sup>381</sup>

Many of the small harms that may be associated with ordinary clinical care, such as bruising at the site of a blood draw or a mild infection, may not warrant compensation because the injury itself either will resolve spontaneously or will be cured with treatment alone. For such small harms, treatment sufficiently minimizes the risk of future harm and cures the harm already done to the subject without the need for compensation. There is no need for financial compensation in these cases because it is unnecessary to make the subject whole.<sup>382</sup>

Distributive justice, which is based on the sharing of the benefits and burdens of research, also requires treatment (but not compensation) in these cases where the injury is slight, because the burden is so light that the subject alone is expected to bear it without the need to distribute the burden any further. An analysis under reparative justice reaches the same conclusion because, where the harm is small, treatment is all that is necessary to repair the harm done. These three justifications for compensation reach the same result in the case of small harms because the subject has not suffered an injury that compensation is necessary to cure—proper medical care is sufficient. Of course, if the required medical treatment is billed to the participant, compensation may be owed to cover the cost of care.

For injuries that persist,<sup>383</sup> are severe, disabling, or cause death, compensation may be required because medical treatment alone does not cure the injury caused. This is the case where the injury has some enduring effect that, as a consequence leads to ongoing medical or economic harm, such as the cost of future medical care, diminished earning capacity, or lost wages.<sup>384</sup> In those cases, nonmaleficence provides a justification for compensation because there is a substantial risk of further medical and financial harm to the subject if some form of compensation is not provided.<sup>385</sup> These types of financial risks stemming from a serious injury are foreseeable and should be guarded

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380. *See id.*

381. *See, e.g.,* 45 C.F.R. § 46 (2009); *see also* Grady, *supra* note 205, at 1686.

382. If the subject is compensated for his time and inconvenience, such small harms may also be accounted for in the amount of that payment.

383. Meaning they require ongoing care or result in lasting impairment.

384. Henry et al., *supra* note 115, at 4.

385. *See supra* Part II.

against as part of the initial risk minimization requirements before a study may go forward.<sup>386</sup> Distributive justice requires compensation in these cases because the cost of a severe injury, including medical care and lost wages, may be more than one individual can bear, but is relatively light when spread across all of the beneficiaries of biomedical research.<sup>387</sup> Compensatory justice also requires compensation for this type of harm because it was incurred due to participation in a socially beneficial activity.<sup>388</sup> Finally, reparative justice counsels in favor of compensation in cases of severe injury or death because treatment alone will not make the injured party whole.<sup>389</sup> The loss in the case of a severe injury or death is greater than the physical loss and it must be treated accordingly.

In light of the moral justifications for providing compensation for research related injuries, it may be permissible to limit compensation to those injuries where treatment alone is insufficient to repair the damage that has been done. It is reasonable for a compensation system, therefore, to limit recovery to cases of serious injury, disability, or death.

#### *D. Remedy*

Determination of an appropriate remedy provides the ability to tailor the compensation provided to the injury suffered.<sup>390</sup> There are two broad categories of remedy that are applicable in the research injury context: treatment and compensation. As discussed briefly above, prompt treatment of research injuries is required by the principle of nonmaleficence because the failure to provide treatment creates a grave risk of future harm. Prompt treatment is relatively uncontroversial as a remedy and is provided by many institutions that do not otherwise provide compensation for research related injuries.<sup>391</sup>

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386. *See supra* Part II. *See also* ASS'N FOR THE BRIT. PHARM. INDUS. ET AL., INSURANCE AND COMPENSATION IN THE EVENT OF INJURY IN PHASE I CLINICAL TRIALS (June 2012) <http://www.abpi.org.uk/our-work/library/guidelines/Pages/clinical-trials-insurance.aspx>; *See also* Medicines for Human Use (Clinical Trials) Regulations, 2004, S.I. 2004/1031, art. 3, ¶ 15(5)(i) (U.K.) (providing for damages in the case of severe or disabling injuries).

387. *See supra* Part II.

388. *See supra* Part II.

389. *See supra* Part II.

390. *See generally* FEINBERG, *supra* note 369 (discussing the development of no-fault remedies in light of the reasons for the creation of various no-fault compensation programs).

391. *See* Resnik et al., *supra* note 37, at 6; *see also* LEWIN GROUP, CARE/COMPENSATION FOR INJURIES IN CLINICAL RESEARCH (Feb. 3, 2005) (on file with the author).

Remedy is both the product of the preceding three elements (cause, type, and degree) and a policy judgment rooted in the justifications for the provision of compensation. In calculating what remedy is appropriate, it is necessary to ask whether there are any complications in the chain of causation present at the time of the injury that might provide a reason for downward deviation in the amount of compensation paid.<sup>392</sup> Furthermore, the type and degree of injury will influence the amount of compensation that is required. Monetary remedies can be broken down broadly into two types: economic and non-economic. Economic remedies are those that compensate for actual economic harms, such as lost wages, costs of care, or loss of future earning potential. Non-economic remedies, however, compensate for intangible harms such as pain and suffering. The different bases for compensation lead to different conclusions with respect to economic and non-economic remedies.

### 1. Economic Remedies

Both the principle of nonmaleficence and the principles of distributive and compensatory justice support the provision of economic remedies. Financial harm flowing from medical harm is a foreseeable risk subject to mitigation and thus creates a duty in nonmaleficence.<sup>393</sup> Financial harm that would not have occurred but for the subject's decision to participate in biomedical research is subject to compensation under the theory of distributive or compensatory justice.<sup>394</sup> The tort doctrine of strict accountability aligns with the bioethical principle of nonmaleficence and provides some support for the allocation of economic damages to injured research subjects. In its longer form, strict accountability is phrased as "strict accountability for harms within the scope of risks distinctive to an actor's conduct or activity."<sup>395</sup> It reflects a judgment "that an actor, even though not at fault, should be liable for harms and risks distinctive to the actor's conduct or activity."<sup>396</sup> This principle is particularly informative in the case of research related injuries, where there is a strong normative reason to reallocate the risk of injury from the party on which it falls (the injured research subject), to another appropriate actor. In this case, the principles of nonmaleficence and distributive and compensatory justice suggest that the cost of injury

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392. See HART & HONORÉ, *supra* note 273, at 180 (detailing how abnormal circumstances that are present at the time of the injury, rather than being incorporated in to the causal framework, are instead taken into account when determining what damages are owed).

393. See *supra* Part II.

394. See *supra* Part II.

395. KEETON ET AL., *supra* note 260, at 609.

396. *Id.*

should be reallocated to sponsors, institutions, researchers, and the public generally. This reallocation of costs is in part possible because the conduct of the duty bearers is socially valuable and will “survive in the marketplace even at the higher price that includes the cost of compensating for harms done.”<sup>397</sup> It also limits compensation to injuries arising from conduct that is “within the risk” of the socially beneficial activity.<sup>398</sup> This forces decision makers to ask whether the type of harm that occurred is of the sort that the policy allocating risk was designed to accommodate. For example, an injury due to an adverse reaction to an investigational drug is within the risks of biomedical research, while a road accident on the way to the clinic arguably may be excluded.<sup>399</sup>

Distributive and compensatory justice, by contrast, are better aligned with a variation on the “welfare principle” of tort remedies. The welfare principle spreads the costs of socially beneficial conduct so that society, rather than the entity that caused the harm, bears some degree of the cost of the injury caused.<sup>400</sup> The aim of the welfare principle is not complete repair of the harm done, but rather the maintenance of a certain baseline standard of economic welfare.<sup>401</sup> This principle counsels that the aim of public compensation for the incidental harms of socially beneficial conduct should not necessarily aim to make the injured party “whole,” but rather, it should ensure that he or she is not further injured or left below a socially acceptable baseline.<sup>402</sup> This principle can be seen at work in countries that choose to incorporate research related injuries into a broader medical compensation scheme, such as Sweden and New Zealand.<sup>403</sup> In those countries, all medical injuries are generally compensable, but compensation is pegged at a capped percentage of the individual’s actual economic losses. Because care is provided through national health systems, the economic losses consist of lost wages and lost future capacity.<sup>404</sup>

Both nonmaleficence and distributive or compensatory justice counsel that careful attention should be paid to the underlying

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397. *Id.* at 610.

398. *See supra* Part III.A.

399. *See* HART & HONORÉ, *supra* note 273, at 80. It should be noted that in the case of a road accident there is also another, more proximate, duty bearer in the form of the negligent driver.

400. KEETON ET AL., *supra* note 260, at 612.

401. *Id.*

402. *See id.*

403. *See supra* Part I (discussing Sweden and New Zealand’s compensation systems).

404. *See supra* Part I.

condition of the subject and the type and degree of the injury in determining what economic damages are owed. The goal of economic damages in this context is not to put the subject in the best position possible, but rather to mitigate the financial risks of research participation and to ensure that the participant is no worse off than if he or she had decided to forego research participation and instead seek standard of care treatment. Alternatively, compensation may be used to ensure a baseline level of economic welfare. Analysis of causation will, therefore, have some influence on the remedy that is appropriate because reduction in the amount of any payment may be justified when the participant's underlying condition or some other additional cause contributed to the participant's morbidity or mortality.<sup>405</sup> Type of injury also affects the determination of the appropriate remedy because, as mentioned above, some types of injury are not likely to be cured by monetary compensation.<sup>406</sup> Similarly, degree of injury is an important consideration because more severe injuries will require a greater degree of compensation in order to place the subject in as good a position as he would have been in had he decided to forego research participation.

In order to take all of the appropriate factors into account, a number of countries rely on their statutory frameworks for determination of damages in personal injury (tort) cases to set the amount of compensation owed in medical injury cases.<sup>407</sup> Factors considered may include the severity of the trial participant's underlying illness, the type of injury suffered, lost wages, and lost earning capacity.<sup>408</sup> Reliance on the tort framework has been controversial in some cases because it may eliminate damages where the patient-participant is already severely ill and therefore does not have economic damages, but nonetheless has suffered a significant injury.<sup>409</sup> Calculation of economic remedies based on a tort measure of damages also risks treating participants differently based on their income.<sup>410</sup> Higher-income research participants would receive more in compensation than lower-income participants who suffered the same

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405. See HART & HONORÉ, *supra* note 273, at 180.

406. See *supra* Part III.B.

407. HELLBACHER ET AL, *supra* note 80; Biskmark & Paterson, *supra* note 46, at 280; Kuroyanagi, *supra* note 68.

408. See Henry et al., *supra* note 115, at 23-24.

409. Kuroyanagi, *supra* note 68. For example, if a participant in a phase one oncology trial is so ill that the participant is unable to work before beginning participation in the trial, and the trial intervention both fails to help the participant's cancer and also causes significant deterioration in the participant's quality of life, then the participant will have suffered harm but will not have an economic harm.

410. See Henry et al., *supra* note 115, at 24-25.

injury. A system based on tort damages would therefore fail to treat like patients alike.<sup>411</sup> Such an arrangement may provide an incentive for researchers and institutions to select participants of low socioeconomic status. Allocation of economic remedies should take account of the likelihood of out-of-pocket costs of medical care to the participant, including future care, lost wages, and any disability or diminished earning capacity. Both long-term and short-term disability benefits should be available. Amounts should be tied to a uniform national standard that adequately compensates individuals for their contribution but also treats like participants alike.<sup>412</sup>

## 2. Non-Economic Remedies

The principle of reparative justice provides the best fit with a requirement to provide non-economic remedies. Non-economic remedies compensate for intangible harms, such as pain and suffering, and are appropriate when the harm suffered is the result of some form of wrongdoing.<sup>413</sup> Nonmaleficence and distributive and compensatory justice provide inadequate support for a requirement to pay non-economic remedies because in those cases wrongdoing is not at the root of the obligation to pay compensation.<sup>414</sup> Requiring the provision of non-economic remedies in the absence of wrongdoing risks deterring the conduct of socially beneficial research activities and might also present unworkable administrative difficulties.

In the case of reparative justice, however, punitive damages may be appropriate both as a deterrent to future wrongdoing and to acknowledge responsibility for the harm that was caused.<sup>415</sup> The “fault

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411. *Id.* at 4.

412. *Id.* at 24. Such a standard should not be a set amount, but should be pegged to a measure that will rise with inflation such as the GS scale. *See also* U.S. DEP’T OF LABOR, DIV. OF COAL MINE WORKER’S COMP., BLACK LUNG MONTHLY BENEFIT RATES FOR 2014 (setting the benefit for all coal miners disabled by black lung disease at “37.5% of the base salary of a Federal employee at level GS-2, Step 1”) *available at* <http://www.dol.gov/owcp/dcmwc/regs/compliance/blbene.htm> (last visited Oct. 20, 2014). *See also* 20 CFR § 726.203(c)(4) (2014); 30 U.S.C. § 901 *et seq.* (2012). Determination of the amount at issue is an appropriate activity for notice and comment rulemaking under the Administrative Procedure Act.

413. *See supra* Part III.B (discussing types of injuries covered and the relationship of type to the justifications supporting compensation).

414. *See supra* Part II.

415. *See, e.g.*, RESTATEMENT (SECOND) OF TORTS § 944 (“The utility of this punitive element in damages is twofold. It may have emotional value to the plaintiff, a matter of special significance in those cases in which the wrong is essentially an injury to the plaintiff’s sentimental interests, as in personal defamation or interference with domestic relations. At the

principle” flowing from reparative justice has been succinctly summarized as, “[w]hen blameworthy conduct causes harm to others, the blameworthy actor ought, in general, to compensate for those harms.”<sup>416</sup> An individual who wrongfully causes harm to another has an obligation to repair the full extent of the damage—in whatever form it may be—and non-economic remedies are appropriate when their application is necessary to make the harmed individual whole. Additional monetary penalties may be appropriate as a deterrent against future bad behavior. As stated above, these cases should be handled through the tort law framework and not through a no fault compensation system.<sup>417</sup>

### *E. Application*

A morally justified compensation framework should be based on principles of nonmaleficence and justice and should take into account all four elements of a well-regulated injury. Within these boundaries, there is considerable flexibility with respect to policy design. Practical implementation concerns such as burdens of proof must be thought through when deciding among potential systems of compensation and determining what type of system might be appropriate. In light of the difficulty of proving causation, especially in clinical trials involving patient-subjects, a preponderance of the evidence standard is appropriate.<sup>418</sup> A no-fault compensation system would cover all injuries that were more likely than not caused by research.<sup>419</sup> This standard should be interpreted leniently in favor of the research participant because the sponsor or institution is likely to have more expertise in the matter and better access to the evidence.<sup>420</sup>

Two systems seem to be the most justifiable in light of both the reasons supporting compensation and the four elements of a compensable research injury. One would be based on a mandatory insurance or self-insurance/indemnity requirement for research sponsors and institutions, and the other would be an administrative specialty court. Each has different strengths and weaknesses and aligns differently with the various relevant considerations.

An insurance or indemnity system is both justifiable and feasible.<sup>421</sup> It has the benefit of allowing cost sharing between the

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same time, the punishment inherent in the remedy will have a more or less deterrent effect upon the defendant.”).

416. KEETON ET AL., *supra* note 260, at 608.

417. Henry et al., *supra* note 115, at 7.

418. *Id.* at 10-11.

419. *See id.* at 3.

420. *Id.* at 10-11.

421. *See generally id.*

research enterprise, which holds the strongest duty in nonmaleficence, and the general public whose broader obligation is based in distributive and compensatory justice. Sponsors or institutions would be required to purchase insurance coverage proportionate to the risk burden of the institution's research profile.<sup>422</sup> This insurance would be used to cover all compensable research related injuries on a no-fault basis.<sup>423</sup> The cost of insurance or self-insurance could feasibly be passed on to consumers of medical products to allow for broader distribution of the burdens.<sup>424</sup>

If administered by an outside insurer, this approach would be rule-based because determinations with respect to the appropriateness of compensation would be made by an insurer relying on a standard definition of "research related injury." An insurance-based plan is thus less flexible in application than an administrative approach. It also has the drawback of being more opaque with respect to its reasoning regarding whether or not an injury is compensable, and as such raises some procedural justice concerns. Finally, insurance may be subject to conflicts of interest because the insurer has an incentive to deny claims in order to maintain a better profit margin.

A variation on the insurance model would be to place the locus of responsibility on research institutions rather than research sponsors. This would account for the wide variation in types of funding for and goals of research. Institutions would have the ability to self insure by setting aside a fund for compensation of research injuries that is commensurate with the risk profile of the research that it conducts.<sup>425</sup> Institutions would also be able to arrange for other duty bearers to contribute to the self-insurance plan. For example, an institution would be able to work out an arrangement for a for-profit company to purchase commercial insurance for their clinical trial, but would be able to either self-insure or otherwise provide assurance that participants in not-for-profit or government sponsored research would be compensated. The institution also has less of a conflict of interest with respect to research subject compensation because it is likely to reap reputational and scientific benefits if subjects feel that the institution is well regulated and accountable.<sup>426</sup>

Placing the locus of responsibility on the institution also has the advantage of working in tandem with existing adverse event reporting

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422. *See id.* at 8.

423. *Id.*

424. *Id.* at 8 (explaining that many pharmaceutical companies incorporate funds set aside for compensation purposes into their research spending).

425. *See id.*

426. *See* London, *supra* note 337, at 933-34; *see also* U.S. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 16, at 61-62.



systems and allowing for greater procedural transparency.<sup>427</sup> Under such a system, either an investigator or a participant could report a suspected research related injury to an institutional administrator.<sup>428</sup> The administrator would seek evidence from both parties and make an initial determination as to whether an injury was research related.<sup>429</sup> All decisions would be made based on a preponderance of the evidence and the standard would be interpreted in favor of the injured subject.<sup>430</sup> An institutional insurance/indemnity plan should provide uniform compensation for medical costs, long- and short-term disability, and a death benefit.<sup>431</sup> Such payments ought to be based on a national measure that does not vary based on the participant's income or the institution where the research is conducted.<sup>432</sup> Such an approach might be more palatable to some institutions than the current practice many undertake of simply settling lawsuits from injured participants before they go to trial.<sup>433</sup>

An administrative court system, by contrast, would place more of the burden on the general public, but could receive some of its funding from the research industry. Such an approach would account for the different ethical obligations held by different stakeholders in the research enterprise. It would have the benefit of being able to apply a standard-based casuistic approach through an expert decision maker. This approach could lead to more predictable and less opaque decision-making that is more readily subject to oversight. In such a system, it may be beneficial to place the burden of proof on the researchers and their sponsors and institutions because those parties are the most likely to have access to the evidence. If the compensation framework is divorced from any type of malpractice or accountability proceedings, requiring researchers to furnish evidence pertaining to a particular participant's care may be easier and will provide the best chance of getting a factual determination of the causes of the injury.<sup>434</sup> It is unlikely, however, that such an approach will be politically

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427. Henry et al., *supra* note 115, at 22-23.

428. *Id.*

429. *Id.*

430. *Id.* See, e.g., GENERAL MOTORS IGNITION COMPENSATION CLAIMS RESOLUTION FACILITY, GENERAL MOTORS IGNITION COMPENSATION FUND PROTOCOL (June 30, 2014) <http://www.gmignitioncompensation.com/docs/FINAL%20PROTOCOL%20June%2030%20202014.pdf>.

431. Henry et al., *supra* note 115, at 24-25.

432. *Id.*

433. A waiver should be required for individuals who choose to accept the payment. See *id.* at 26.

434. See, e.g., Kachalia et al., *supra* note 113, at 400.

feasible given the lack of will to put any compensation system in place over the past several decades.<sup>435</sup> An administrative court system divorced from the institution also raises serious concerns about the burden on research participants<sup>436</sup> and about the equitable sharing of the cost of research injuries.

In light of all of the relevant considerations, an institution-based self-insurance approach combined with a similar requirement for sponsors of research is both the best compensation system and the one that is most likely to be implemented.<sup>437</sup> An institution-based self-insurance/indemnity approach places the burden of compensation on those in the best position to foresee and minimize risks. It also allows for cost sharing between institutions, sponsors and the public to the extent that costs of funding the compensation system are built into either the cost of care at the institution or the cost of the products produced.<sup>438</sup> Furthermore, an institution based insurance/self-insurance requirement is easily compatible with other systems of compensation around the world. This is a consideration of particular importance in light of the amount of international research conducted by sponsors within the United States.

This type of practice already has support at some institutions within the United States and would require less political and regulatory change to implement than the creation of a specialized court or public compensation fund.<sup>439</sup> It also has the benefit of enabling a less burdensome administrative claims process and minimizing bureaucracy thus allowing for efficiency in getting financial compensation to those who need it.<sup>440</sup>

## CONCLUSION

At the heart of an ethically justifiable compensation system is a succinct and appropriate definition of what constitutes a compensable research related injury. That definition should contain the four regulatory elements of causation, type, degree, and remedy. In short,

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435. See, e.g., Henry, *supra* note 13, at 412; see also Alan J. Weisbard, *The Role of Philosophers in the Public Policy Process: A View from the President's Commission*, 97 ETHICS 776, 779-82 (1987).

436. See Genevieve M. Grant et al., *Relationship Between Stressfulness of Claiming for Injury Compensation and Long-term Recovery*, 71(4) JAMA PSYCHIATRY 446, 446 (2014).

437. See Henry et al., *supra* note 115, at 14.

438. See *supra* Part II.

439. See Henry et al., *supra* note 115 at 11, 27.

440. See *id.* at 5. See also Grant et al., *supra* note 436, at 446 (noting that a more stressful claiming process is associated with a longer recovery time).

a compensable injury is a medical injury, caused by the subject's research participation, and is of such a degree that medical treatment alone is insufficient to remedy the harm caused. By using this definition as a starting point, it is possible that, in spite of forty years of inaction, the research community may begin to move toward a comprehensive no-fault approach to compensation of research related injuries. In doing so, the research community in the United States would not only join the ranks of most other countries engaged in significant biomedical research, but would also fulfill a long-neglected ethical obligation.